DRY POWDER LAYERING OF HIGH VISCOSITY POLYMERS USING A FLUIDIZED BED ROTOR GRANULATOR

Martti Ahtola
University of Helsinki
Faculty of Pharmacy
Division of Pharmaceutical Chemistry and Technology
Discipline of Industrial Pharmacy
AstraZeneca
2014

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

Tiedekunta/Osasto˜ Fakultet/Sektion – Faculty Faculty of Pharmacy/Division of Pharmaceutical Chemistry and Technology	Laitos˜ Institution – Department	
TekijäFörfattare – Author Martti Ahtola		
Työn nimi˜ Arbetets titel – Title Dry Powder Layering of High Viscosity Polymers Using a Fluidized Bed Rotor Granulator		
Oppiaine˜ Läroämne – Subject Industrial Pharmacy		
Työn laji Arbetets art – Level Masters thesis	Aika˜ Datum – Month and year 10/2014	Sivumäärä Sidoantal – Number of pages 93

Tiivistelmä˜ Referat – Abstract

The goal of the thesis was to optimize a dry powder layering process that would produce a swelling polymer layer that could work as a base layer for another layer. The GPCG 1 (Glatt) fluidized bed granulator was equipped with a rotor. Such hydrophilic polymers were used for coating that would not be sensible timewise for wet coating methods because of long process time. For design of experiments Definitive Screening was chosen because it works in situations where time is limited and there is high number of parameters. There were six parameters, four related to the equipment settings and two related to the formulation, that were tested on three levels. The results were used to get optimized parameters using a model in MODDE software. The quality of the coating was analyzed by measuring the friability (strain test with fluidized bed granulator), particle size (dynamic image analyzer), density (helium pycnometer and mercurity porosimeter), erosion (size exclusion chromatography), loss on drying (halogen moisture analyzer) and coating efficiency (weighing and loss on drying). Coating was also analyzed also with scanning electron microscopy. The process was robust with regards to sphericity of the coated pellets. In SEM pictures none of the coatings showed complete film formation. Friability method did not show significant differences between batches. Coating efficiency was high for all batches. Correlations between product characteristics were analyzed and some correlations were observed between including correlations between LOD/CE and densities. No correlation between the densities measured with two different methods were seen. Some of the settings in the DOE were too extreme and produced batches that were very difficult to analyze. Two more batches were produced with adjusted settings. This affected somewhat the ability to develop a reliable model. Model development were also affected by insufficient results from erosion tests and because coating efficiency results with water was used. Some stability problems were noticed during design of experiments and chosen equipment limited the scale of settings. Coating material adhered to the surface of the pellets and process could be adjusted by changing the parameters of the DOE. Some correlations were noticed between formulation, equipment settings and coating properties.

Avainsanat – Nyckelord – Keywords
kuivajauhepäällystys, definitive screening, leijupetirakeistin, hydrofiilinen polymeeri

Säilytyspaikka – Förvaringställe – Where deposited

Muita tietoja – Övriga uppgifter – Additional information

Anne Juppo, Katrin Walter ja Susan Abrahmsén Alami

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

Tiedekunta/Osasto Fakultet/Sektion – Faculty Farmasian tiedekunta/Farmaseuttisen kemian ja teknologian osasto	Laitos Institution – Department	
Tekijä Författare – Author Martti Ahtola		
Työn nimi Arbetets titel – Title Dry Powder Layering of High Viscosity Polymers Using a Fluidized Bed Rotor Granulator		
Oppiaine Läroämne – Subject Teollisuusfarmasia		
Työn laji Arbetets art – Level Pro Gradu	Aika Datum – Month and year 10/2014	Sivumäärä Sidoantal – Number of pages 93

Tiivistelmä Referat – Abstract

Pro gradun tavoitteena oli optimoida kuivajauhepäällystysmenetelmä, joka päällystää pelletin turpoavalla polymeerikerroksella, joka voisi toimia pohjakerroksena toiselle päällystyskerrokselle. GPCG 1 (Glatt) leijupetirakeistin oli varustettu roottorilla. Päällystysmateriaalina käytettiin sellaisia hydrofiilisilla polymeereja, joita ei olisi ajallisesti järkevä käyttää perinteisellä menetelmällä alhaisen konsentraation ja siten pitkän prosessiajan takia. Koeasetelmassa käytettiin hypromelloosilaatua HPMC K4M. Koeasetelmaksi valittiin Definitive Screening, joka soveltuu tilanteisiin, joissa aikaa on vähän ja tutkittavia parametrejä on paljon. Kolmella tasolla tutkittavia parametreja oli kuusi, neljä laitteiston asetuksiin liittyvää ja kaksi formulaatioon liittyvää parametria. Saatujen tulosten perusteella pyrittiin saamaan optimoidut parametrit päällystyksen tuottamiseen käyttämällä mallia MODDE-ohjelmistossa. Päällystyksen laatua tutkittiin mittaamalla murenevuutta (leijupetirakeistin rasituskoe), partikkelikokoa (dynaaminen kuva-analysaattori), tiheyttä (heliumpyknometri ja elohopeaporosimetri), eroosiota (kokoekskluusiokromatografia), kuivaushävikkiä (halogeenikosteusanalysaattori) ja päällystystehokkuutta (punnitus ja kuivaushävikki). Päällystystä tutkittiin myös pyyhkäisyelektronimikroskopialla. Prosessi tuotti tasaisesti pyöreitä päällystettyjä pellettejä. SEM-kuvissa ei ollut havaittavissa täydellistä kalvonmuodostusta missään tuotetuista eristä. Murenevuuden tutkimiseen käytetyllä menetelmällä ei havaittu merkittäviä eroja tuotettujen erien välillä. Kaikkien erien päällystystehokkuus oli korkea. Tuotteiden ominaisuuksien välisiä korrelaatioita tutkittiin, mm. kuivaushävikin/päällystystehokkuuden ja tiheyksien välillä. Kahdella eri menetelmällä mitattujen tiheyksien välillä ei havaittu korrelaatiota. Jotkut koeasetelman asetukset olivat liian äärimmäisiä ja tuotettuja eriä oli hyvin vaikea analysoida. Kaksi lisäerää tuotettiin säädetyillä asetuksilla. Tämä vaikutti luotettavan mallin kehittämiseen. Mallin kehittämiseen vaikutti myös riittämättömät tulokset eroosiokokeista ja se, että päällystystehokkuudesta käytettiin tuloksia, jotka sisälsivät veden. Joitain ongelmia havaittiin vakauden suhteen koeasetelman aikana ja valittu laitteisto rajoitti asetuksien mittakaavaa. Päällystysmateriaali saatiin tarttumaan pelletin pintaan ja prosessia pystyttiin säätelemään muuttamalla koeasettelun parametreja. Joitain syy-seuraussuhteita oli havaittavissa formulaation, laiteasetusten ja päällystyksen ominaisuuksien välillä.

Avainsanat – Nyckelord – Keywords
dry powder layering, dry powder coating, hydrophilic polymers, HPMC K4M, definitive screening, fluidized bed rotor granulator

Säilytyspaikka – Förvaringställe – Where deposited

Muita tietoja – Övriga uppgifter – Additional information

Anne Juppo, Katrin Walter ja Susan Abrahmsén Alami

ABBREVIATIONS

API = active pharmaceutical ingredient

app = apparent density

ATEC = acettl triethyl citrate

avg = average pore diameter

bulk = bulk density

CE = coating efficiency

CL = coating level

CR = controlled release

DOE = design of experiments

fri = friability

LOD = loss on drying

MALS = multi-angle light scattering

MCC = microcrystalline cellulose

MLR = multiple linear regression

PEG = polyethylene glycol

por = porosity

PSD = particle size distribution

pyc = pycnometric density

RI = refractive index

SEC = size exclusion chromatography

SEM = scanning electron microscope/microscopy

sph = sphericity

TES = time-controlled exposion system

T_g = glass transition temperature

TMA = thermo mechanical analysis

1. INTRODUCTION

Various coating methods have been used for oral pharmaceutical preparations. Nowadays coatings are used more than ever and the repertoire of coating methods is becoming more diverse all the time. This diversity is the result of the advancement of the technology and it has also triggered the development of new excipients. New coating method can use new excipients, or new mixtures of excipients and/or new processing equipment, also a standard coating method can be used in a new way.

The reason for coating can be something as simple as creating a nice appearance for the product, but the coating can also be the most important component of the product - e.g. by making correct dosing of the active pharmaceutical ingredient (API) possible. For example, a coating can mask the unpleasant taste or smell of the API in an oral product. A coating can also be used to create nice looking products that are easily recognized. In some cases, one or several of the necessary excipients of the product can render the product hard to swallow. A coating can then increase the flowability and reduce the stickiness of the product (Yamamoto et al. 2013). A coating can be used to protect the API from air, moisture and light and hence increases the shelf life of the product. During handling and packaging a coating may protect the product from abrasion. In cases such as combination products the API can even be introduced directly into the coating. Coating can be used to provide a continuous release of the API as well as providing target to a specific region of the gastrointestinal tract.

Controlled release (CR) systems that use coating and layers have been developed to enhance the bioavailability of oral dosage forms. These systems can use polymers with swelling and eroding properties for the coating or the matrix/core of the system. An example of this type of CR system is a tablet that has a core that swells and erodes and a permeable and elastic coating that holds the system together (Deshpande et al. 1996). The API is released from the expanded matrix and the tablet is suspended in the GI before it disintegrates (or loses integrity). Swelling system can also have a non-elastic and

permeable or semi-permeable coating that ruptures when the layer or coating underneath it starts to swell (Hata et al. 1989; Bussemera et al. 2003; Dashevsky and Mohamad 2006). This type of system can be called time-controlled explosion system (TES) and it creates a lag to the release of the API.

In this thesis the coating substrate was an inert cellulose based core and the coating was used to create a pellet with possibilities to alter the swelling and erosion properties but also to create a sub-coating for another coating layer. To induce swelling of the coating layer high viscosity hydrophilic polymers are used (Gao and Meury 1996; Li et al. 2005). When the viscosity of these polymers is high, only low concentrations can be used in the coating solution. With a low concentration of spray solution a long process time is required to achieve high coating levels (CL). A literature search indicates that dry powder coating may be suitable method to produce swelling and eroding pellets.

The aim of this thesis is to optimize the dry powder layering method for coating of pellets using traditional fluid bed rotor granulator equipment and traditional coating excipients in a new way. Compared to conventional liquid based coating method the dry powder coating method would be faster and simpler. An additional advantage could be that the method would be better used with water sensitive materials.

2. CONTROLLED RELEASE

The coating layer, achieved in this thesis, should swell and erode in a similar way as a swelling and eroding matrix. To achieve, this hydrophilic polymers such as cellulose ethers have been commonly used for both tablets and pellets (Alderman 1984; Tahara et al. 1995; Kavanagh and Corrigan 2004). For sustained release tablets the release rate of the drug is dependent on the infiltration rate of the medium if the drug is water soluble and the erosion rate if the drug is poorly soluble in water. Erosion rate and thus release rate of the poorly

soluble drug is controlled by the viscosity of the polymer. Erosion rate decreases when the molecular weight of the polymer increases. Increase in molecular weight increases the extent of swelling.

Pellets, tablets and capsules can be coated with modified release coating that delays the release of the drug (Bodmeier and Paeratakul 1991). Pellets can be compressed into tablets or they can be filled in to capsules (Bodmeier 1997). Coating creates a film that delays the release of the drug from the core. Dependent on the choice of polymer the release can be pH-dependent or pH-independent (Bodmeier and Paeratakul 1991). Coating has to be flexible because otherwise it will lose the sustained release when the pellets are compressed into a tablet (the film cracks). The tablets that are compressed from coated pellets or capsules that are filled with coated pellets can be coated themselves to create a two-step MR system. Extended release pellets or tablets can be created with mixture of insoluble and soluble coating polymers (EP 1711169 A1). Pellets can have multiple coatings that have different properties (e.g. pH-dependent, swellable layer and enteric layer; or drug layer, diffusion layer and retention layer) (Gazzaniga et al. 1994, Heng et al. 1999).

Swelling polymers respond to solvent or swelling agent by changing their physical alignment from glassy to rubbery (Colombo 1993; Colombo et al. 2000). Swelling polymers can be used in matrices and in push layers of so-called osmotic pump tablets (Malaterre et al. 2009). Hydration decreases the glass transition temperature (T_g) of the polymer and relaxes the polymer chain. When increasing the temperature above the glass transition temperature the amorphous material transform from hard state into a molten or rubbery state (ISO 11357-2:2013). The hydration rate is dependent on different qualities of the polymer used. Relaxation enables the polymer molecules to get closer each other. Chemical structure, concentration of the gel layer and viscosity determine the strength (and firmness) of the gel layer. The swelling front is the boundary between glassy and rubbery matrix regions. The erosion front is the interface between the rubbery matrix region and dissolution medium. The outer hydrated layer will erode as it turns more dilute (Aulton and Taylor 2007).

When the gel layer is fully hydrated the forces between water and polymers become stronger than polymer-polymer forces and the layer starts to erode (Alderman 1984). By adjusting the thickness and density of the coating the lag time of API release (if there is a drug layer under the coating) can be controlled (Kao et al. 1997). The viscosity of a polymer solution is related to the molecular weight but it is also dependent on the molecule structure and chemical characteristics: shape, rigidity of the polymer chain and electrostatic charge density (Williams 2007b).

The erosion rate of the coating tells how long it takes before the polymers start to detach from the gel layer that is formed after the pellet comes in contact with aqueous solution (Colombo 1993). Erosion begins after the gel layer has swollen to a point where the linkages between polymers start to break. The erosion rate is dependent on the density and porosity of the coating. Density and porosity are affected by the structure and particle size of coating polymers as well as on the parameters of the coating process.

Density and porosity could affect how the solution (e.g. water) gets absorbed by the coating. A more porous coating absorbs the solution faster because it has more surface area. Swelling is also faster because the solution gets into the coating faster. Density also affects the size of the pellets and the amount of swelling. A denser coating swells more compared to the original volume. Denser coating leads to less friability and to better handling. Porosity affects how the coating works as sub-coating during later processing (e.g. adhesion and penetration of new material into the coating).

3. POLYMERS FOR CONTROLLED RELEASE

Polymers and plasticizers are the most commonly used materials in coatings (Hogan 1995). The most popular coating polymers are cellulose derivatives, acrylic polymers and different co-polymers. Coating materials have to be chosen so that they fit their purpose, can be used with the processing equipment and are economically and ecologically sensible. There can be variations of properties between manufacturers and batches and thus it is important to test new batches appropriately and develop a robust coating method that withstands environmental variations.

Hydrophilic polymers are polymers that absorb water. Hydrophilic polymers can be used for example to form physical gels, to modify surface properties and to create a controlled release and/or delivery system for API (Williams 2007a). Hydrophilic polymers that are used for matrices can be divided into three groups: cellulose derivatives, non-cellulose natural or semisynthetic polymers and polymers of acrylic acid (Alderman 1984; Salsa et al. 1997).

Hydrogels, that are cross-linked polymeric networks, can be applied to different kinds of drug delivery routes: oral, rectal, ocular, epidermal and subcutaneous (Peppas et al. 2000).The polymers that are used for this thesis' dry powder coating process are high viscosity hydrophilic polymers. These high viscosity polymers are hoped to have similar properties as a coating layer as they would have in matrix: gelling, swelling and effect on drug dissolution.

PubChem (2013) search with "Polymer" reveals that polymers are a loose group of molecules that are formed by thousands or even millions atoms connected to each other. The molecular units (monomers) of polymer are connected with covalent bonds. Polymers usually consist of organic components and their origin can be natural, semisynthetic or synthetic (Williams 2007a). By one definition polymers have molecular weight over 25 000

g/mol and they consist of molecule units of similar structure (Sperling 2006). Oligomer is a polymer with a relatively small amount of monomers. A homopolymer consist only one type of monomers whereas a copolymer has two or more different kind of monomers (Peacock and Calhoun 2006; Strobl 2007a).

Many of the commercial polymers have different grades (Handbook of Pharmaceutical Exipients 2009). These are different versions of the polymer that have the same basic structure, but there are variations in molecular weight, substitution, branching, steric configuration, preferable chain orientations, interconnections, chemical defects etc. If no suitable polymer grade is available, wanted characteristics for an excipient can be achieved by mixing different polymer grades (Peacock and Calhoun 2006). Polymer particles that are too large can be micronized into smaller particles (Pearnchob and Bodmeier 2003c).

Thermoplastic polymers turn softer or harder when temperature changes (Peacock and Calhoun 2006). Thermoplastic polymers are linear and they have only non-permanent bonds to other polymers. This can be exploited by adjusting the coating and curing temperatures.

If the polymer chains or polymer's branches are long enough there can be entanglement between the polymer chains (Peacock and Calhoun 2006). Entanglements are temporary connections/links between the polymers. Branches can also form cross-links between polymers.

There are three different physical forms a polymer can have: rubbery amorphous, glassy amorphous and crystalline (Peacock and Calhoun 2006). In amorphous state the polymers are not organized. In crystalline state the polymers are in symmetrical order. Usually there is no clear cut between glassy amorphous and crystalline states and they co-exist as a "semi-crystalline" state. Semi-crystalline state consists of tiny crystals that are called crystallites that are surrounded by amorphous polymers. These amorphous polymers between crystallites connect crystallites to each other. Plasticizer works so that it gets in

and in-between the polymers and loosens the structure and transforms the mixture to a more amorphous form.

The glass transition temperature and plastic deformation properties of the coating material dictate the success of the dry powder coating (Sauer et al. 2013). If the product temperature is higher than glass transition temperature of the polymer, the polymer is in the rubbery amorphous state (Peacock and Calhoun 2006; Williams 2007b). In the amorphous state the molecular chains have space to move, vibrate, twist and rotate. When the temperature falls below T_g the space between chains is reduced and the thermal motion is limited to vibration. By increasing the processing temperature the coating material becomes more liquid-like and less viscous. This increases the capillary forces and enhances the spreading of the coating material on the substrate surface. Mechanical forces of the coating process (fluidization and rotation) cause deformation of the coating material, which adds its own aspect to the adherence and coalescence of the coating.

3.1 Hydroxypropyl methylcellulose

Cellulose derivatives are polymers that have a cellulose chain of varying length and varying kind of substituents. The derivatives are made from cellulose that is obtained from trees and cotton and cellulosic polymers are widely used because they have good swelling properties, low toxicity, low cost and easy access (Colombo 1993; Williams 2007b). Cellulose derivatives are popular excipients in pharmaceutical products and cellulose ethers are the most used polymers in film coating (Hogan 1995; Mastropietro and Omidian 2013). Cellulose derivatives are used in all the common pharmaceutical dosage forms, but biggest areas are tablets and capsules. Hydroxypropyl methylcellulose (HPMC) is the most common cellulose derivative used in prescription medical products.

HPMC is manufactured from cellulose in a reaction with methyl chloride (CH_2Cl_2), propylene oxide (CH_3CHCH_2O) and sodium hydroxide (NaOH) as a base catalyst (Salsa et al. 1997; Mastropietro and Omidian 2013). The substituent groups of hydroxypropyl

methylcellulose are O-methoxy and O-(2-hydroxypropoxy) (Ph. Eur.; Handbook of Pharmaceutical Excipients 2009). The 2208 grades of HPMC have 19 – 24 % methoxy substitution and 7 – 12 % hydroxypropyl substitution. HPMC is a white powder or granulate material. It is hygroscopic after drying and dissolves in cold water. Polymer's properties are dependent on chain length and the relative substitution of methyl and hydroxypropyl, which are represented by different grades. The number of the methyl groups dictates the gel properties such as firmness and gelling temperature of HPMC. The bigger the part of methyl groups is the firmer the gel is. HPMC has many functional possibilities in formulations such as binder, film-coating agent, suspending agent and emulsifier. The non-tackiness of HPMC makes it easy to process.

3.2 Carbomers

Carbomers are high-molecular-weight polymers with acrylic acid chain that are cross-linked with alkenyl ethers of sugars or poly-alcohols (Handbook of Pharmaceutical Excipients 2009; Ph. Eur.). 56 – 68 % of carbomer's molecular weight is carboxylic acid. Carbomers are white, fluffy powders that swell in water and in other polar solvents. Carbomer forms a hydrogel when it's in contact with water or alkaline solution (Muramatsu et al. 2000). Hydrogel formation happens when the carboxylic groups of carbomer hydrate. Carbomers have been used as matrix formation material with cellulosics and to some extent as coating material. Different grades have different molecule weights and different degrees of cross-linking (Muramatsu et al. 2000).

3.3 Plasticizers

"Plasticizers are low molecular weight materials which have the capacity to alter the physical properties of polymer to render it more useful in performing its function as a film-coating material" (Hogan 1995). Plasticizers can be categorized in three groups: polyols, organic esters and glycerides. To get between/inside polymers and to weaken the intermolecular polymer-polymer binding forces, the plasticizer usually should have

chemical similarities with the polymer it plasticizes (Felton and McGinity 2002). Weakening intermolecular binding forces increases the mobility of the polymers and results to the lowering of the T_g of the polymer mixture.

Higher processing temperatures can also be used to increase the mobility of coating polymers, but when plasticizer is used lower processing temperatures can be applied (Peacock and Calhoun 2006; Terebesi and Bodmeier 2010). Addition of too much plasticizer can lower the T_g too much and cause stickiness of the coating during processing (Cerea et al. 2004, Kablitz and Urbanetz 2009). Some stickiness is wanted for the polymer particles stick to the surface of the substrates but it has to be well balanced so that it does not cause agglomeration of the pellets and sticking to container walls (Smikalla et al. 2011). T_g and melting temperature of plasticized material can be measured beforehand with DSC.

Also the water acts as liquid plasticizer and affects the dry powder coating process by functioning as a liquid plasticizer and by creating temporary capillary forces between polymer particles and the substrate surface (Kablitz and Urbanetz 2007; Kablitz et al. 2008; Sauer et al. 2007; Smikalla et al. 2011). Because water can function as a plasticizer it is important to measure the loss on drying value of the product pellets and check if the drying is sufficient. Capillary forces disappear after the liquid plasticizer has penetrated into the polymer particles. After this van der Waals forces and electrostatic forces cause cohesion and adhesion of the particles.

Macrogols are group of polyethylene glycol polymers (Ph. Eur.). Number after “Macrogol” or “PEG” indicates the average relative molecular mass. In this thesis PEG 400 was used. PEG 400 is a clear, viscous, colourless and hygroscopic liquid. It is miscible with water.

Acetyltriethyl Citrate is used as a plasticizer in pharmaceutical coatings (Handbook of Pharmaceutical Excipients 2009). It is used for immediate release coatings and different types of modified release coatings. Acetyltriethyl Citrate is a clear, odorless, practically colorless oily liquid.

4. COATING OF PELLETS

Within pharmaceutical domain the word “pellet” describes a group of systematically produced and geometrically defined agglomerates that can be manufactured with different methods from variety of starting materials (Ghebre-Sellassie 1989). The popularity of pellets is based on their good handling properties and multiple purposes of use. The ease of handling of pellets is result of spherical form and good flowability of the material. Because pellets are easy to handle and flow well in the coating equipment, they usually have good coating properties. In the pharmaceutical industry pellets are often used to create multiple unit dosage forms (Bodmeier 1997). Pellets can contain active pharmaceutical ingredient or they can be inert cores. Pellet cores can be coated or they can be mixed with API-pellets.

The manufacturing of pellets can be called “pelletization” and its definition according to Ghebre-Sellassie (1989) is: “an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free-flowing, spherical or semi-spherical units, referred to as pellets.” Properties of the coated pellet are dictated by the size, shape, morphology and composition of the core pellet. Probably the most used pelletization technique is extrusion/spheronization (Zhang et al. 2009). Depending on the planned purpose of pellets, there are many different physical and functional properties to evaluate: weight, porosity, size, compactability, deformability, tensile strength, density etc.

For pellets a traditional coating method is one that uses atomization and spraying of dispersions or suspensions of organic and/or aqueous solvents of polymers (Sauer et al. 2013). These liquid based methods are called “wet coating methods”. The dispersion or solution used for wet coating method consist of coating polymer and possibly some other excipients and active pharmaceutical ingredient. This solution or dispersion of excipients is then sprayed on the substrates. Water or organic solvent is then evaporated and the particles of the dispersion get closer to each other. The particles are separated by a thin layer of

solvent when they start to lose their shape and the gaps between particles get even smaller. Finally the particles diffuse into a film.

Pellets can also be coated with different kind of dry powder coating methods. Dry coating methods use mainly the same components (coating polymer, excipients, and spray liquid) for the coating as the conventional liquid based coating methods, but they are used differently.

Graham Cole describes coating as a painting process that gives the substrate a uniform look (1995b). According to Hogan (1995) film coating is “a thin polymer-based coat applied to a solid dosage form such as a tablet, granule or other particle”. Coating is an important part of production in pharmaceutical industry, but it is widely used in other industries too and thus many of the applications used for pharmaceutical products have been originally adopted from food industry (Cole 1995b). Thickness of coating in pharmaceutical products is usually between 20 μm and 100 μm (Hogan 1995). Coating thickness depends on the purpose of coating, coating materials and the coating substrate. These same factors also affect, which coating technique is chosen and how it is used.

Many coating methods for tablets and pellets still use organic solvents for polymers (Cole 1995a). Organic solvents can have acute and/or long-term toxicities and thus they can be hazardous to the operator and to the environment (Medscape 2013). Depending on the solvent the toxic effects can cause a variety of illnesses for example different types of cancer and neurological problems. Usage of some of the organic solvents (e.g. CFCs, carbon tetrachloride, methyl bromide and methyl chloroform) is partly or completely banned in industrial use and the usage of some solvents is controlled and limited by national departments and international treaties (The Montreal Protocol 2009; OSHA 2013).

When organic solvents are used in a coating process there has to be a solvent recovery system and all of the processing equipment has to be flameproof (Cole 1995b). Restrictions, increasing costs and potential hazards of organic solvents combined with new

knowledge of coating methods and materials and the development of better coating equipment have led to usage of aqueous coatings when possible.

In aqueous coating processes polymers are formulated into aqueous colloidal dispersions (Bodmeier 1997). Aqueous dispersions are less toxic, safer and cheaper than organic solvents, but the drying period of aqueous coating methods takes more time and energy than with organic solvents (Sauer et al. 2013). Some APIs and excipients are sensitive to water or they are soluble only in organic solvents, which limit aqueous coating possibilities. Films produced with aqueous coating methods can have stability problems (Terebesi and Bodmeier 2010). Aqueous coating dispersions of polymers such as hydroxypropylmethylcellulose acetate succinate (HPMCAS) often are of low concentrations and therefore the liquid consumption is high, if high coating levels are wanted. The coating solution has to be manufactured before coating process and the coating process is time consuming and due to the low concentrations and large amounts of liquid that have to be evaporated. Additionally, spray nozzle limits the rate of liquid that can be atomized during a certain time interval (Dixit and Puthli 2009).

4.1 Dry powder coating of pellets in fluidized bed

Dry powder coating was developed to overcome the solubility, instability and time problems of aqueous coating (Vuppala et al. 1997; Maruyama et al. 1998; Obara et al. 1999). The dry powder coating method produces a coating on a solid particle by feeding polymeric powder and by spraying an atomized liquid mixture (containing for example API, plasticizer and liquid substance) simultaneously. The dissolution step is thereby removed and replaced with step that creates coating by plasticizing the polymer and softening the material by raising temperature and by mechanical processing while layering the material on substrates.

The dry powder coating was designed to create a sustained release layer or enteric film using same equipment and same material as organic and aqueous methods before (Obara et

al. 1999). Methods from both Vuppala and Maruyama and Obara used liquid plasticizer and in the latter method water was sprayed on the pellets during the curing process so the methods developed were not literally dry, but water usage was minimal compared to aqueous coating methods. Water was used during spheronization to smoothen the coating and to enhance the film forming.

Dry powder coating consist of similar steps as traditional coating: pre-treating the coating material, the coating of the substrates and a drying or a curing phase (Sauer et al. 2013). Dry powder coating process can also be divided in four or five steps: (preparations), wetting of the cores, coating, spheronization and drying. The specifics and durations of these phases may vary and there are no clear borders between phases. Important to note is that everything happens in the same equipment and that the process is seamless. Although dry powder coating with fluidized bed equipment uses less liquid than organic liquid or aqueous based coating methods, the same three basic phases for coating as for traditional methods are present: solid, liquid and air (Dixit and Puthli 2009).

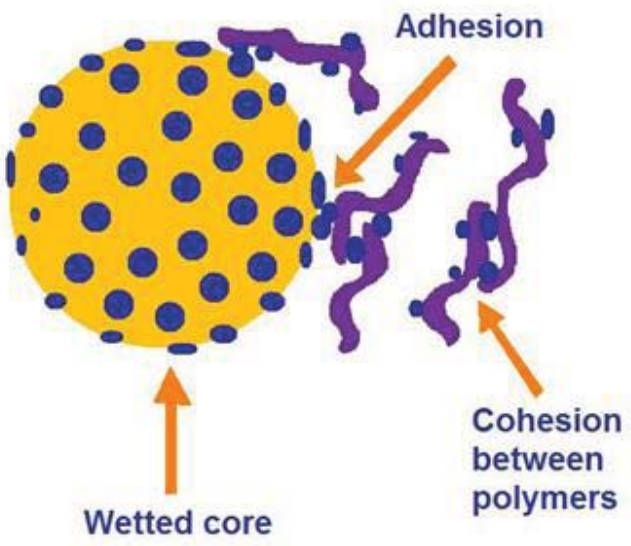


Figure 1. Wetting of core pellets and cohesion and adhesion of polymers.

During the wetting phase the core beads are wetted with liquid that can be for example pure water, binder solution or plasticizer solution. Wetting enhances the adhesion of the dry powder during the beginning of the coating phase by creating capillary forces (Figure 1), but also increases the agglomeration tendency of core beads (Dixit and Puthli 2009). The core beads have been inserted into the product container during preparations. In addition to this, dry powder is inserted to powder feeder, plasticizer liquid is connected to a flexible plastic tube (which is connected to the spraying pistol) and the liquid is pumped so that the tube is completely filled.

During the coating phase the wanted amount of plasticizer solution and dry powder are simultaneously introduced into the fluid bed. Spraying of plasticizer can be started before the powder feeding (wetting phase). Powder adheres to the surface of the cores with the help of liquid on the surface of the cores and the plasticizer that alters the properties of polymer. To enhance the adherence the coating temperature can be adjusted to conditions near the glass transition temperature of plasticized polymer. T_g of mixture can be estimated with Fox equation or Gordon-Taylor equation if the T_gs of components and formulation is known (Sauer et al. 2013).

Fox equation is

$$\frac{1}{T_g} = \sum_{i=1}^{n} \frac{W_i}{T_{g,i}}, \quad (1)$$

where W is weight fraction.

Gordon-Taylor equation is

$$T_g = \frac{w_a T_a + k w_b T_b}{w_a + k w_b}, \quad (2)$$

where T_a and T_b are glass transition temperatures and w_a and w_b are weight fractions of the components a and b respectively

T_g can be measured for example with differential scanning calorimetry (DSC) or thermo mechanical analysis (TMA) (Kablitz et al. 2006; Kablitz 2007). TMA measurement technique usually requires that the coating is casted on a plate or sphere, and then peeled off and measured.

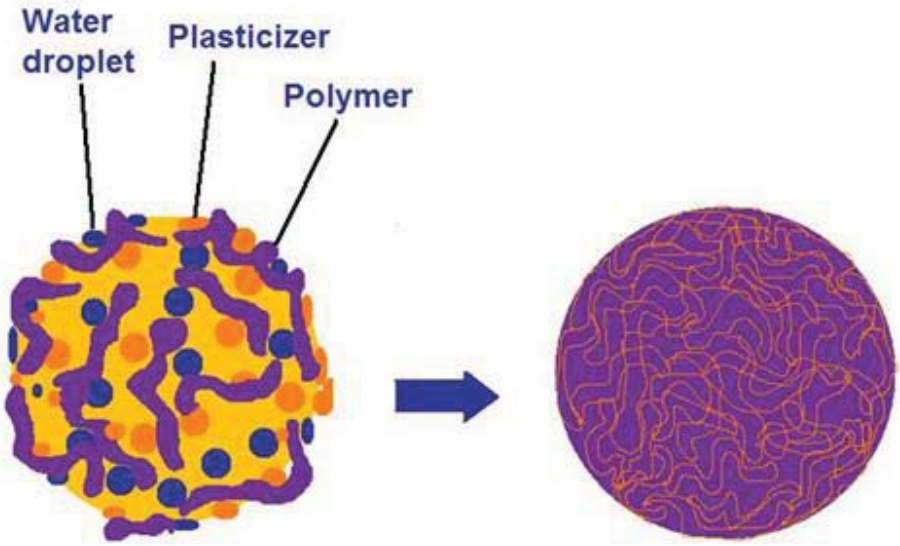


Figure 2. Formation of layer from polymer, plasticizer and water.

According to Sauer et al. (2013) the film formation of the powder layered film on the surface of the substrate can be categorized in three steps: coalescence and sintering, leveling of the coating material (densification, reduction of the empty spaces and smoothening the surfaces) and cooling and hardening (Figure 2). For amorphous materials the coalescence happens usually at temperatures above the T_g of the polymer (Bellehumeur et al. 1998). During the spheronization step the polymer layer becomes more homogenous (coalescence) and the new pellets get rounder (smoothening) as the name of the phase implies. Extra liquid is evaporated during the drying phase. Drying and spheronization can be done simultaneously.

4.2 Coating level and coating efficiency

Coating level refers to the mass of coating compared to the whole weight of the product and in the case of pellets it can be determined by Equation 3.

$$CL = \frac{M_{Coating}}{M_{Core}+M_{Coating}} \quad (3)$$

M is the mass in the equation.

Coating level may have to be changed if the coating polymer changes, but properties of coating are wanted to be kept constant.

To create an enteric coating it is generally thought that a higher coating level is required for dry powder coating compared to an aqueous coating method (Sauer et al. 2013). A higher coating level is needed, because coatings from dry powder coating have a more porous structure than coatings from wet coating methods (Kablitz and Urbanetz 2007). A porous structure can be beneficial if good swelling properties of the core or coating are wanted (Omidian et al. 2005).

Coating efficiency (CE) tells how much of the coating material that is inserted into the equipment ends up into the final coating. Efficiency should be as close to 100 % as possible. If material is lost during coating, the loose material can affect the process negatively. Negative consequences of low coating efficiency can be unpredictability, coating that has properties that do not meet the requirements. If the coating includes an API, the dosage can be wrong. Coating efficiency is defined as the actual mass the pellets gain during coating (M_a) divided by the theoretical mass that coated pellets could gain if there was no loss of coating material during the coating and curing processes (M_t) multiplied with 100 (Kablitz et al. 2008).

When evaluating the process parameters of dry coating process with a 2^{5-1} factorial design, Kablitz and Urbanetz (2013) chose high coating efficiency as the most important critical quality attribute (CQA) for their process, because the thickness of the coating/film is crucial to delaying the release from coated pellet. In the research they tried to recognize critical process parameters (CPP) of dry powder coating and decided on those that had an effect on the CQA. They found coating temperature, curing temperature, feeding/spraying rate, air flow and rotor speed to be CPPs.

Coating efficiency of dry coating process is often of interest, because it is usually lower in dry coating processes than in traditional wet coating processes (Kablitz and Urbanetz 2013). This is most likely because the adherence of dry powder on to the substrate surfaces is harder to achieve in dry processes that use significantly less liquid than conventional coating methods. Coating efficiency of dry powder coating method is also affected by many other parameters such as the ones mentioned in the above paragraph.

4.3 Manufacturing equipment for dry powder layering

For the coating process fluidized bed rotor granulator Glatt GPCG1 is used. GPCG stands for Glatt-Powder-Coater-Granulator (Glatt 2013; Figure 3). The rotor system is intended for coating pellets and crystals, but it can also produce pellets (granulation) sized from 50 μm to 5 mm.

Figure 3. GPCG 1 with powder feeder and peristaltic pump.

A fluidized bed of solid material has similar properties as a fluid (Dixit and Puthli 2009). In pharmaceutical applications fluidization is usually achieved using air as gas. The high velocity air separates particles and transforms the particle mass to fluid-like state (Jones and Percel 1994; Parikh et al. 1997). The fluidized particles are in turbulent motion which resembles boiling of a liquid. Fluid bed processors are used for agglomeration, coating and drying of pellets (Fukumori and Ichikawa 2006; Glatt 2013). Typical fluidized bed processors are top spray, bottom spray and tangential spray. These types are differentiated by the direction of spray. Other applications are tumbling fluid bed and spouted bed. Tumbling fluid bed has a rotor and spouted bed has draft tube (Wurster insert).

In a rotary fluid bed processor there is a spinning disc at the bottom of the product container that adds spinning motion to the cores as they are coated using spraying and

powder feeding (Dixit and Puthli 2009). This way the agglomeration (or coating) happens simultaneously with spheronization. The rotation and following spiraling motion creates more particle-particle and particle-wall collisions than would be possible using fluidization only. The shape of the fluidized bed is dependent on the fluidizing air volume per hour and rotary speed of the disc. For optimal coating conditions the bed should be have "rope-like" movement (Figure 5). Schematics and basic functions of a Glatt-type rotor granulator are depicted in Figure 4.

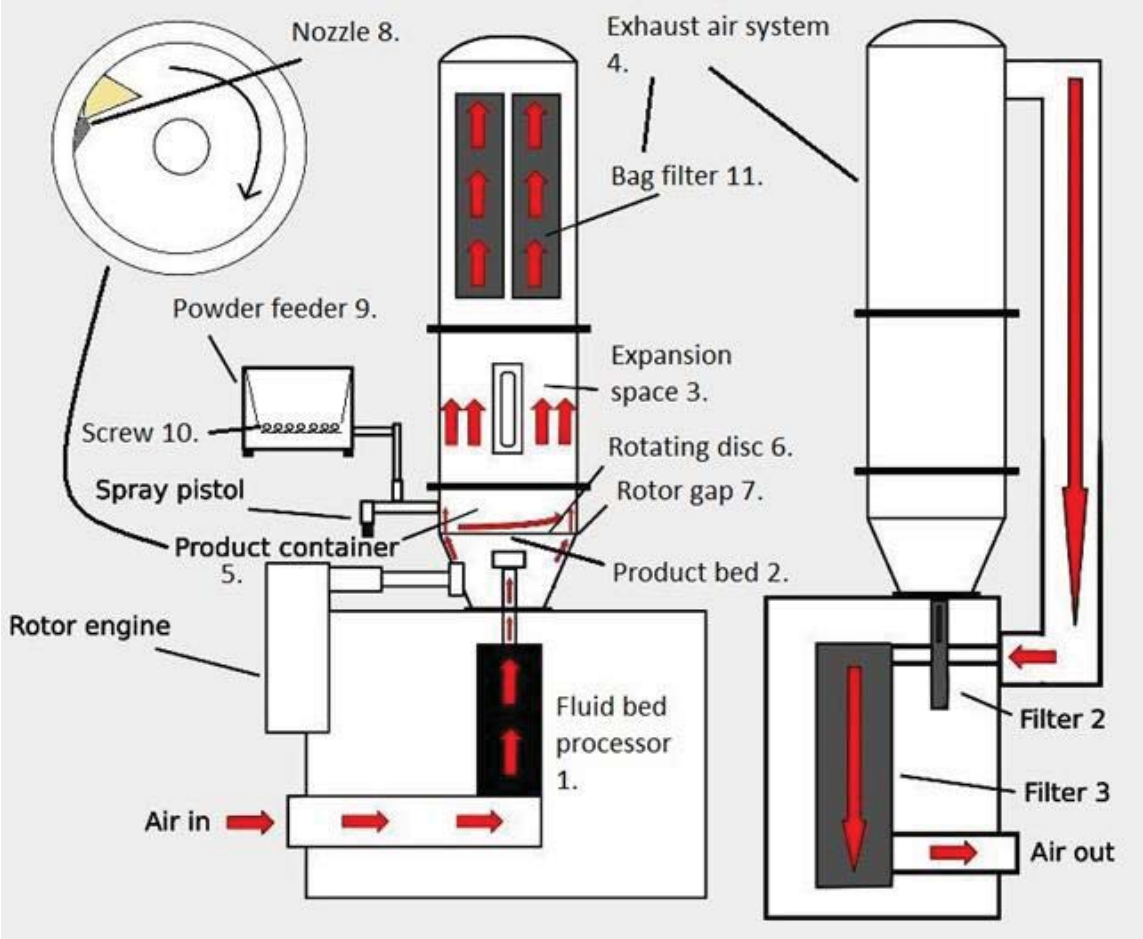


Figure 4. Picture depicts the schematics of a Glatt-type fluidized bed rotor-granulator.

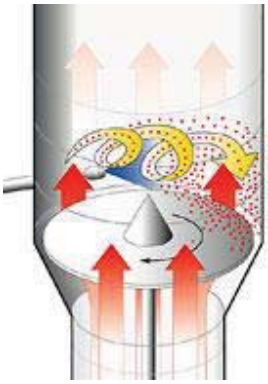


Figure 5. Picture depicts rope-like movement of particles in rotary fluid bed with tangential spray (Glatt 2013)

All fluid bed processes require conditioning of the process air and the same principles are applied in laboratory scale (e.g. with GPCG 1) as on industrial scale (Olsen 1989). In laboratory scale the inlet air can be taken from the room and conditioning controls the temperature and the humidity of the air. Fluid bed processor (Figure 4: 1.) warms up the processing air, directs it through the product bed (Parikh et al. 1997). Once the air has gone through the product bed (Figure 4: 2.) and the expansion space (Figure 4: 3.) it enters the exhaust air system (Figure 4: 4.) which includes filters and a mechanism to get the air out of the system.

In a rotor granulator the product container (Figure 4: 5.) has a rotating disc (Figure 4: 6.) at its base (Parikh et al. 1997). Speed and height of the rotor can be controlled as can be the rotor material and properties of the rotor (Dixit and Puthli 2009). Smooth rotor plate that is used for dry powder coating, does not have much adhesion but as a downside it has less spheronization effect on particles (Pisek et al. 2000). Adjusting rotor height adjusts the rotor slit width or the gap between rotor and the container wall (Figure 4: 7.). In rotor granulator the fluidizing air comes up from the gap and fluidizes the particle bed. Velocity of the product bed can be controlled by the height of the disc and by the fluidizing air volume (fluidizing flow). The spiraling motion of the fluid bed is generated by three forces: rotating pushes the product towards walls (tangential force), fluidizing flow pushes the

product up (vertical force) and gravity pushes it down and to the middle of the plate (gravitational force) (Dixit and Puthli 2009).

The velocity air flow is high enough to get the particles in motion (Parikh et al. 1997; Dixit and Puthli 2009). Incipient velocity and entrainment velocities (or minimum and terminal velocities) are the lower and upper limit of fluidization. When the air velocity is over incipient velocity there are air bubbles going through the bed mixing the particles. The velocity can be increased until the entrainment velocity is reached and the particles get carried through the expansion chamber and away with the air. Between the incipient and entrainment velocities the bed is fluidized. If there are different particle sizes in the bed (e.g. core beads and loose coating particles) it is possible that the entrainment value of the smaller particle is less than the incipient value of larger particles. In this kind of situation the smaller particles (powder) are lost with the fluidizing air, if they do not adhere to coating substrates.

With GPCG 1 the air removal is done by central vacuum. Filters remove fine particles from the processing air before the air leaves the fluid bed equipment (Parikh et al. 1997). Expansion space is also partly responsible of removing particles from air that are leaving the processor by simply applying gravitational force on pellets that are rising upwards. When the rotor granulator is used the particles do not usually rise upwards during the coating, unless the fluidizing flow is too high (over the entrainment velocity) and/or the polymer particles do not adhere to the surface of coating substrates. There are bag filters (Figure 4: 11.) of different materials and for different particle sizes. The filters usually have more than one bag that can be shaken during the coating process so that the process does not have to stop during the cleaning.

The fluidized particles go past the spray nozzle (Figure 4: 8.), which is tangential to the bed and sprays atomized liquid on the particles (Parikh et al. 1997). Part of the pistol that is in the product chamber should usually be completely inside the product bed (Dixit and Puthli

2009). The pistol can be easily removed and replaced with a plug during the process (Olsen 1989).

GPCG 1 has a three-way air-atomizing nozzle which means that it handles the dry powder, liquid and atomizing air (Figure 6). Atomizing air nozzle is the most popular kind of nozzle in fluidized bed systems because the droplet size can be controlled independently of the flow rate, the nozzle can operate with low spray rates and it does not cause that much of evaporation of the coating liquid (Olsen 1989). The tip (Figure 6: 9.) of the nozzle can be changed to different diameter. This affects the velocity of spray. By adjusting the screw (Figure 6: 10.) the width of the spray can be changed.

Atomizing pressure air tube (Figure 6: 8.), peristaltic pump tube that pumps plasticizer solution (Figure 6: 7.) and the screw conveyor that feeds powder (Figure 6: 1.) are connected to the spray pistol. Atomizing air is divided to the middle layer and outer layer of the pistol. The powder is pushed forward in the outer layer of pistol by the air pressure from atomizing air. Powder comes out from around the spray nozzle (Figure 6: 2.). The liquid moves forward by the force of peristaltic pump in the inner layer (Figure 6: 5.). Air atomizes the liquid when it comes out of the tip.

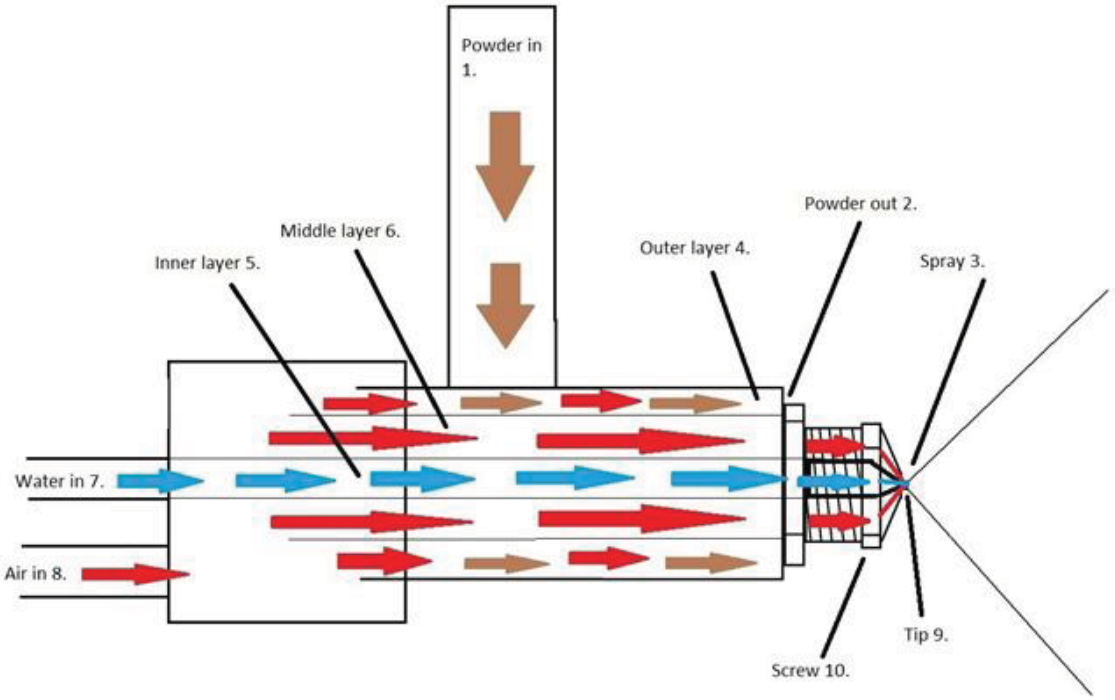


Figure 6. Picture depicts movement of powder, water and air in a spray pistol with three-way-nozzle.

Spraying breaks the liquid into multiple droplets that are in a gas (Olsen 1989). Spraying enables spreading of the liquid on an as big area as possible. On the other hand the small droplet size of the spray can predispose the liquid to evaporation by the heated fluidizing flow. Droplet size can be adjusted by changing the atomizing pressure. The spraying has three phases:

1) Expansion and cooling of compressed air as the pressure drops to the pressure of the fluid bed chamber
2) Liquid forms into separate drops and surface area of liquid increases
3) Droplets travel until they evaporate or get in contact with product surface

The powder is inserted to the powder feeder (Figure 4: 9.) before the process starts. At the bottom of the funnel there is a screw (Figure 4: 10.). Rotation speed of the screw can be

controlled and the rotation speed controls the rate of powder feeding. At the end of the screw conveyor the powder falls to the outer layer (Figure 6: 4.) of the spray pistol. At this point the powder might be partly affected by the atomizing pressure in the spray pistol by "sucking" the powder out from the feeder as a result of pressure difference. In GPCG 1 the powder feeder and spray liquid pump are not part of the standard equipment and they can be changed to suitable models.

5. PREVIOUS EXPERIENCES WITH DRY POWDER LAYERING FOR CONTROLLED RELEASE APPLICATIONS

Obara et al. (1999) investigated the practicality of dry powder coating with micronized HPMCAS using lab scale equipment. They also examined the performance of the coating, coating efficiency and stability of the coating. The process included a coating phase with simultaneous powder feeding and liquid spraying and a curing phase where water or HPMC solution was sprayed on the coated beads for 5 minutes and the beads were heated until the outlet temperature reached 50°C. Triethyl citrate (TEC) was used as plasticizer. The article mentions that the team has tried to use HPMC as a coating polymer, but without success. HPMCAS provides good softening properties and gastric retention was achieved using it as the coating polymer.

Pearnchob and Bodmeier (2003a) did research on dry powder coating using Eudragit RS, ethylcellulose and shellac as coating polymers and GPCG 1 (Wurster insert) as coating equipment. They studied the mechanism of film formation, process and formulation variables and compared dry powder coating to conventional liquid based coating methods. A mixture of plasticizer and HPMC was sprayed simultaneously with powder feeding. A mixture was used because spraying pure plasticizer had led to sticking and agglomeration. Various plasticizers were tried at 40% w/w based on polymer weight, e.g. triethyl citrate , acetyltributyl citrate (ATBC) and acetylated monoglyceride (AMG). They noted that film

formation was mainly achieved during the curing phase. Extended release was achieved with Eudragit RS and ethylcellulose. Enteric coating was achieved with shellac and reduction of particle size was suggested. For extended release (from pellets) with dry powder coating a higher coating level was required but it was noted that a shorter coating time was achieved with dry powder coating.

With the right polymer and good plasticization coating level can be lowered to 10 % and still have extended release even when using a dry powder coating method (Terebesi and Bodmeier 2010). By choosing the right polymer and plasticizer(s) for the extended release coating it was possible to achieve 10 – 15% coating levels depending on the solubility of the API. Dry powder coating was found to be possible completely without water. By adjusting the plasticizer level, the film composition was improved.

Pearnchob and Bodmeier (2003b and -c) tried to optimize a dry powder coating processes with micronized ethylcellulose and Eudragit RS. They investigated how coating and curing process parameters and formulation factors affected coating properties (release and stability) and whether extended release was achievable. Adhesion was started with plasticizer/HPMC solution. TEC and AMG were used as plasticizers. Good adhesion was achieved but a curing process was required for the film formation to commence. Coatings had good stabilities. Overcoating with plasticizer/HPMC mixture (smilar to what Obara et al. 1999 did) was tried, but it did not change the release profile and it was determined to be unnecessary.

During literature search no custom grade for dry powder coating was found. Dry powder coating has previously been done with smaller size (micronized) polymer grades that are less than 3% of the substrate's size (Sauer et al. 2013). Because of the objectives of this thesis the grades used have larger particle sizes (for example ~20% compared to the substrate size) than those used in previously published research. This can affect the thickness of the coating (Pearnchob and Bodmeier 2003c). Large particles can create a porous layer that has good swelling properties (Omidian et al. 2005).

In literature about dry powder layering different values for the plasticizer amount in the coating formulation can be found. Some examples are 10 – 40% (Obara et al. 1999; Pearnchob and Bodmeier 2003a and -b), 10 – 30% (Bilancetti et al. 2010) and 15 – 35% (Kablitz 2007) of plasticizer compared to polymer weight. These percentages are for enteric coating formulations and mainly with triethyl citrate or distilled acetylated monoglyceride as plasticizer and very small particle size coating polymer. Plasticizer was used in such amounts that film was formed during curing phase. With completely different particle size of polymer and different objectives for the coating, not much can be made use of these values.

Good spreading of liquid excipients (wetting agent and plasticizer) on polymers enhances the adhesion and cohesion of polymers and that is why spreadability of liquid additives has been researched with contact angle measurements (Obara et al. 1999; Kablitz 2007; Smikalla et al. 2011). Lower contact angle of the liquid additive on the surface of the polymer should lead to higher coating efficiency. Smikalla et al. (2011) used sessile drop method and drop shape analyzer to measure contact angles. They found relationship between high contact angle and low coating efficiency. Coating efficiency improved when wetting agents had lower contact angles. Wetting of the polymers is important to the adherence of first layer of polymers on the substrate surface. The other polymers adhere to this first layer. PEG400 was found to have a poor coating efficiency with ethylcellulose (55.2%) and that the poor CE was found to be related to its high contact angle (Smikalla et al. 2011).

Kablitz and Urbanetz (2007) characterized the film formation of dry powder coating. The formulation was 75% (w/w) HPCMAS and 25% plasticizer (35:15 TEC/Myvacet®). Films with the same formulation were cast from organic solutions and T_g of these films were examined with thermal analysis. Based on the knowledge gained from the thermal analysis, the coated pellets (25% CL) were cured at different temperatures. Effect of curing temperature and curing time to enteric resistance was examined. Drug release was limited

by the increasing curing temperature until the T_g of the plasticized coating polymer. Higher temperatures did't not decrease release rate any further. It was determined that the T_g of the plasticized polymer is a key parameter.

In their 2007 study Kablitz and Urbanetz also observed film formation in the inner part of coating layer by looking at SEM pictures of the cross-sections of the produced pellets. Film formation was suspected to be the result of spraying plasticizer 30 seconds on the core pellets before starting the powder feeding. This caused the plasticizer concentration to be higher on the inner layers of coating. Because of higher plasticizer concentration T_g is lower in the inner parts of the coating and the film formation begins from the inner layers. This should be taken into consideration during morphology observations with cross-section images. The objective should be a homogeneous spreading of plasticizer and uniform properties throughout the coating.

Sauer et al. 2007 tried to prevent migration of a highly water soluble API to the film by using dry powder coating. They used Eudragit L 100-55 as the coating polymer and TEC as the plasticizer. A primer subcoat (PEG3350) was used for powder adhesion and film formation. Primer reduces the surface tension of the substrate surface and improves the adhesion of dry powder. Sauer and McGinity (2009a) examined the influence of excipients on melt viscosity, surface tension and film formation of dry powder coating using Eudragit L 100-55 as coating polymer, TEC as plasticizer and PEG3350 as primer. TEC reduced the polymer viscosity and increased the surface free energy of the coating polymer. PEG3350 reduced the viscosity of the coating polymer, but it did not increase the surface free energy of the coating polymer.

6. OBJECTIVES

General objectives for this series of experiments with this particular dry powder coating method are to have a faster, easier and less energy-consuming and thus a more ecological coating method than comparable conventional coating methods with aqueous dispersions or organic solutions. Objective of this thesis is to coat inert cores with hydrophilic polymer and create a swelling and eroding layer. The series of experiments should lead to a robust coating method with possibilities for case sensitive adjustments that could be used to create layers that can be used in variety of controlled release pellet systems.

The thickness and density of the layer should be specific and adjustable. Depending on the coating polymer and coating level, the complete coating time should be considerably shorter when compared with aqueous (or organic) coating methods. Formulation is chosen so that the polymer layer turns into a swelling and/or eroding gel-layer when it is in contact with an aqueous solution. The swelling and erosion of the gelling layer should happen to an extent and at a rate that can be controlled. Layer should also be uniform and it should be able to endure further processing.

The coating powder formulation should be such that it a) flows nicely in the feeder funnel b) is not sticky in the stainless steel screw feeder and c) creates a polymer layer with above mentioned properties. The optimal coating level should be determined as a function of swelling rate, density, morphology and particle size distribution based on the properties of pellets that have ~30% coating level.

7. MATERIALS AND METHODS

7.1 Materials

The coating polymers tested were hydroxypropyl methylcellulose (HPMC) grades K100LV (2208, 100 cps) Premium CR (Methocel®, Dow) and HPMC K4M (2208, 4000 cps) Premium CR (Methocel®, Dow). Carbomer grades were 971P NF and 71G NF (Lubrizol®).

The plasticizer used was macrogol (infusion grade polyethylene glycol, PEG 400). Acetyl triethyl citrate (ATEC) and water were also tested as plasticizers in single experiments.

The microcrystalline cellulose core beads were CP-507 (CelPhere, Asahi Kasei Chemicals Corporation, Tokyo, Japan) and Cellets 500 (Pharmatrans Sanaq AG, Switzerland). MCC is purified, partly depolymerized cellulose type (Ph. Eur.). It is white, odorless, tasteless and crystalline powder of porous particles (Handbook of Pharmaceutical Excipients 2009). MCC has high water-containing properties.

HPMC 3cP (Methocel E3-LV, Colorcon Limited, Kent, England) was used as a binder during pretesting. It was used both as a 3% and a 6% water solution during the coating phase.

7.2 Methods

The coating was done with GPCG 1 (Glatt GmbH, Binzen, West Germany). Powder was fed with a screw conveyor (Secudos, G+K Fuchs GmbH, Wiehl, Germany). The plasticizer liquid was pumped with a peristaltic pump (505U Watson+Marlow GmbH, Rommerskirchen, Germany) and the tube type was Masterflex 060409-16 H20 (Cole-Palmer, USA). Spray nozzle diameter was 0.8 mm and the screw was set to 3.

Parameters of coating should be customized for every formulation, because even the slightest differences in the surface structure, bonding forces, sizes or shapes can affect the coating efficiency (Guignon et al. 2003). The six parameters that were chosen during the initial experimenting period were rotor speed, spheronization phase temperature, feed rate, ratio of feed rate and spray rate, percentage of plasticizer and batch size. Parameters of coating equipment that were kept constant during DOE included (at least): gap size, temperature of wetting and coating phase, atomizing pressure and other spray settings, times of wetting and spheronization phases, fluidization air flow, rotor type (material) and filter. Characterization methods have been chosen based on reliability, reproducibility, availability of equipment, time consumption and simplicity of use.

7.2.1 Design of experiments

Finding the right process parameters can be challenging, because the process has many variables and the process parameters have to be readjusted according to the formulation changes.

Design of experiments is used to make statistically sound decisions about the formulation and process parameters (Antony 2003). A parameter can have a straight effect on the result but there might also be combinatory effects with one or several other parameters. These are called first- and second-order effects and together they complicate the optimization of parameters. The pre-experimentation phase could be considered to be a random screening that was based on knowledge about previous runs with somewhat similar formulation. There is also information available about previous designs with different parameters and objectives (Vertommen and Kinget 1997; Kablitz and Urbanetz 2013). Random screening gave some indications of parameter limits and this knowledge could be used for DOE.

The type of DOE chosen for this thesis was definitive screening, because it is optimal in situation where time and resources are limited but there is large number of variables (Jones and Nachtsheim 2011). Definitive screening can be used to analyze quantitative factors on

three levels in conditions where both first-order and second-order effects are present. The main effects are completely independent of the second-order effects (two factor interactions and quadratic effects) (Appendix 3). The second-order effects have correlations with other second-order effects but they are not completely confounded. The design of definitive screening has a fold-over structure (Table 7). This means that there are two consecutive runs with same parameter the center point and other parameters at the opposite extremes.

Table 7. Fold-over structure of the design: the red and green circles are highlighting the fold-over-system (the center-point parameter) and opposite extremes of other parameters, respectively.

Run Order	Temp (C)	Rotor (rpm)	Plasticizer (%)	Powder feed rate (g/min)	Powder/spray ratio	Batch size (g)
7	55	500	1	8	0,5	500
1	55	100	30	14	1	1000
4	80	300	1	14	1	500
8	30	300	30	8	0,5	1000
12	30	100	15,5	14	0,5	500
13	80	500	15,5	8	1	1000
3	30	500	30	11	1	500
11	80	100	1	11	0,5	1000
6	80	100	30	8	0,75	500
9	30	500	1	14	0,75	1000
2	80	500	30	14	0,5	750
5	30	100	1	8	1	750
10	55	300	15,5	11	0,75	750
14	55	300	15,5	11	0,75	750

Table 8. Process parameters of DOE batches.

Batch	Temp (°C)	Rotor speed (rpm)	Plasticizer (%)	Powder feed rate (g/min)	Powder/ spray ratio	Batch size (g)
DOE1	55	100	30	14	1	1000
DOE2	80	500	30	14	0.5	750
DOE3	30	500	30	11	1	500
DOE4	80	300	1	14	1	500
DOE5	30	100	1	8	1	750
DOE6	80	100	30	8	0.75	500
DOE7	55	500	1	8	0.5	500
DOE8	30	300	30	8	0.5	1000
DOE9	30	500	1	14	0.75	1000
DOE10	55	300	15.5	11	0.75	750
DOE11	80	100	1	11	0.5	1000
DOE11.3	80	200	1	11	0.5	1000
DOE12	30	100	15.5	14	0.5	500
DOE12.2	30	200	15.5	14	0.5	500
DOE13	80	500	15.5	8	1	1000
DOE14	55	300	15.5	11	0.75	750

There were six quantitative variables that were tested on three levels (Table 7, Table 8 and Table 9). Definitive screening requires $2n + 1$ runs where n is the number of the parameters. The design consisted of 14 runs, which were executed in randomized order. The 14^{th} run of the design was replication of the run with all parameters at the center-point. This was done to get an estimate of experimental error (Appendix 3). Excluding these two center point runs all the other runs have one parameter at center point and all the other parameters at extremes.

The responses of DOE were:

- Friability
- Particle size distribution [Span: $(x_{90} - x_{10})/x_{50}$]
- Density (Apparent, Bulk and Pycnometric)

- (Dissolution rate/Erosion)*
- Loss on Drying
- Coating efficiency

x_{10}, x_{50} and x_{90} are density distribution values given by QicPic. 10% fractile (x10) is the diameter that corresponds to 10 % of the particles (50% fractile, x50 to 50% and 90% fractile, x90 to 90%).

*Erosion rate was not measured for all of the batches and thus it wasn't used for the models/optimization.

Table 9. DOE parameters and their levels

Parameter	Min. value	Center point	Max. value
Spheronization temperature	30 ˚C	55 ˚C	80 ˚C
Rotor speed	100 rpm (200 rpm)	300 rpm	500 rpm
Plasticizer weight (PEG400) compared to coating polymer weight	1 %	15,5 %	30 %
Powder feed rate	8 g/min	11 g/min	14 g/min
Powder feed rate - liquid spray rate -ratio	0.5	0.75	1.0
Amount of core beads	500 g	750 g	1000 g

Randomization of run order and analysis of design's results were conducted with MODDE 9.1 (Umetrics). Definitive screening design was imported from Excel file that contained parameters and values in an order that was described in article from Jones and Nachtsheim (2011; Table 7). Results from characterization methods were imported to design file. Models were fitted with multiple linear regression (MLR) approach. Optimization tools of MODDE were used to find out optimized parameters.

7.2.2 Particle size distribution and shape of the particles

The particle size distribution (PSD) and sphericity of the excipients and the products were characterized with a dynamic image analyser QicPic (Sympatec, Germany). QicPic was installed with gravity feeder GRADIS and vibratory feeder VIBRI. GRADIS is basically a funnel through which the analyzed particles fall from the vibrating feeder and go pass the camera system. QicPic can take up to 450 pictures per second and its software is able to analyze the particle sizes and shapes of individual particles.

The software turns every detected particle into vector graphics so that individual particles can be analyzed (Figure 14). Software also gives particles shape and size values, which can be used to categorize the contents of the batch. This feature can be used for example to remove agglomerates and debris from the analysis. Unfortunately the software has some problems with its interface and the utilization of some the features is hindered.

The analyzing technique can affect the particle size because there can be segregation within the batch or in the sample. Also the core beads can be segregated during storing, handling and distribution. QicPic should work independent of size, shape, surface morphology or physicochemical properties of the substrate. QicPic works well even with small amounts of sample. The same sample can be re-measured, because measuring is non-destructive and sample can be stored after measuring. If storing is not wanted, the sample is vacuumed automatically away from the equipment.

During analysis 5 – 15 ml of unsieved pellets were inserted to the VIBRI feeder. The sample volume determines the amount of particles measured and increases the accuracy of measurement. The sample size was increased for samples that had a visually noticeable wide particle size distribution or relatively big particles. Measuring was done three times from three different samples for each batch. Some testing was required to find optimal parameters for every pellet batch. When possible, the same settings were used for all DOE samples. Following parameters were adjusted: outlet width (after drop and before camera),

feed rate/vibration of VIBRI, gap width between the sample funnel and the slope of VIBRI and the measuring range of the camera.

7.2.3 Morphology of the pellet surface and cross-section

Morphology of the pellet surface and the cross-section of the pellets were analyzed with scanning electron microscope (SEM). Samples were mounted on 12 mm diameter adhesive carbon tabs, G3347N, Pk100, Agar scientific. The samples were sprayed with gold in a vacuum with a Cressington Sputter Coater 108 Auto (Cressington Scientific Instruments Ltd., Watford, England) with Argon gas. Spraying was done twice for 100 seconds at 20 mA and 0.3 bar. The samples were analyzed with Quanta 200 SEM (FEI, Hillsboro, Oregon, USA) and xT microscope control software. Imaging was done in a vacuum and at high voltage (10 kV). Images were taken at ~100x and ~400x magnifications.

Sequences of SEM-pictures were taken for every batch produced during DOE: shape of pellet, close-up of coating and cross-section of coating. Pictures were also taken after aliquots of the batches had been cured in an oven for 24 hours. Curing was done at 80°C, because the GPCG 1 equipment was calibrated so that 80°C was the highest inlet temperature that could be used.

7.2.4 Erosion of the coating

The erosion of coating was analyzed through dissolution studies and the samples were analyzed with size exclusion chromatography with dual multi-angle light scattering and refractive index detection (SEC-MALS/RI) equipment. 500 mg of pellets were placed in 500 ml of 0.1 M sodium phosphate buffer. pH of buffer solution was 6.8 and it was GMP quality. Two separate vessels for batches were used. Dissolution equipment was SR8PLUS Dissolution Test Station (Hanson Research Corp., Chatsworth, CA, USA). SR8 is an USP apparatus 2, the paddle apparatus. Temperature of the solution was set to 37°C and paddle speed was 50 rpm. Sampling was done with a pipette and 0.5 ml samples were taken after

5, 15, 30, 45, 60, 90, 120, 150, 180 and 240 minutes (10 samples in total). Samples were stored in glass vials.

HPMC concentration of the samples from dissolution testing was analyzed using TSK gel column $GMPW_{XL}$, 7.8 mm ID * 30.0 cm, with particle size of 13 µm (TOSOH corporation, Japan). Refractometer was an Optilab rEX (Wyatt Technology, Santa Barbara, CA, USA) that was fixed at 35°C. The MALS instrument was DAWN® EOS™ (Wyatt Technology, Santa Barbara, CA, USA). The flow rate during the analyses was 0.5 ml/min. The mobile phase was 10 mM NaCl with 0.02% NaN_3. Volume of the injected samples were 100 µl. The refractive index increment used was 0.136 ml/g. The results were processed with Astra 5.3 software (Wyatt Technology, Santa Barbara, CA, USA).

7.2.5 Friability

Friability is tested to assess the pellets' ability to withstand further processing. There is no recommended method for friability testing of pellets in pharmacopoeias. There's no official requirement value for the friability of coated pellets either. The friability testing was done with an in-house fluidized bed equipment with a Wurster insert (different equipment than for the coating). This setting should emulate quite well the particle-to-particle and particle-to-wall frictional forces of further processing that the coated pellets might have to endure. The pellets go through a test run without coating or spraying.

100 g of sieved product pellets were inserted in the equipment. Parameters for testing were: fluidizing flow 40 m^3/h, atomizer pressure 2.5 bar, inlet temperature 50°C and processing time 10 minutes. 500 ml Duran flask was inserted to the equipment so that the outlet air from the equipment goes through the bottle. Small particles accumulate into the bottle. Bottle was weighed before and after the process. Deduction of the bottle weights was used as an indicator of friability.

Friability was calculated by weighing the pellet mass before every experiment and the mass the bottle (cyclone) gained during the fluidization. Mass of the material in bottle was calculated as mass percentage of the weighted pellet mass. Measurements were done three times for every batch with individual samples. Friability was also measured for the CP-507 core beads.

7.2.6 Loss on Drying and Coating efficiency

Water determination is conducted according to USP Method III (gravimetric). This procedure is called loss on drying (LOD). LOD of the pellets is analyzed with HR73 Halogen Moisture Analyzer (Mettler Toledo GmbH, Greifensee, Switzerland). Halogen Moisture Analyzer does a gravimetric measurement of the sample and uses halogen dryer unit to heat the sample (Mettler Toledo 2001). Moisture of the sample vaporizes when heated and weight of the sample is monitored throughout the heating.

Samples were taken after wetting, coating, spheronization and drying phases or every 10 minutes to see how moist the material is during processing. LOD of the final product pellets was also measured. 1 - 3 g of pellets was inserted to analyzer. Sample was heated 10 minutes at 110°C.

The coating efficiency (CE) was calculated from weighting results after the coating (actual mass) and from the theoretical mass the coated pellets should have had if no material was lost during coating or no water was bound to the coating. The following Equation 4. was used:

$$CE = \frac{M_a}{M_t} \times 100\ \%, \tag{4}$$

where Ma is actual mass of coating and Mt is theoretical mass of coating.

7.2.7 Density and porosity

The density and porosity of the pellet are affected by the amount and the structure of the coating. If the plasticization of coating polymer has succeeded and the coating and spheronization temperatures have been at the right level, a dense and uniform film will be formed. Two different density measurement techniques were used; helium pycnometer and mercury porosimeter.

The helium pycnometer was Micromeritics AccuPyc 1330 (Norcross, GA 30093, USA). True density and pycnometric density are equal if the helium gas can access all the open and closed pores of the pellets (USP). If the helium can only access the open pores, pycnometric density is equal to apparent density. The volume of the sample is calculated from the change in pressure when gas expands from sample chamber to expansion chamber. Samples were accurately weighed before and after density measurements. AccuPyc uses the given weight and volume of sample to calculate the density. The sample is purged ten times and volume is measured ten times. Then an average volume is calculated from these ten runs. It cannot be known with certainty that helium doesn't also fill closed cavities of core and coating. The mercury porosimetric method was used to get knowledge about only the open pores.

Mercury porosimetric measurements were out-sourced to SWEREA (Swedish Research), where the measurements were done with AutoPore (Micromeritics Instruments Corporation, Norcross, GA 30093, USA). About 1 g of material from each batch (DOE11.3 and DOE12.2, but not DOE11 and DOE12) was used for measurements. Porosity and density were measured at low pressure and high pressure. The measuring technique of mercury porosimetry is based on capillary law, where mercury works as a non-wetting and non-reactive liquid (Micromeritics 2001). Mercury fills the cavities of sample when pressure is increased. The higher the pressure gets the smaller the filled pores are. There are two different chambers in the porosimeter: one chamber for low pressure measurements and other chamber for high pressure measurements.

8. RESULTS AND DISCUSSION

8.1 Pre-tests

A number of pre-tests were produced before variables and parameters were chosen for Design of Experiments (Appendix 1). Different kinds of formulations and process parameters were tested during these experiments. Tested coating polymers were Methocel K15 CR, K100LV and K4M and Carbopol 971P NF and 71G NF. Different kinds of binder solutions were tested, for example 6% HPMC 3 cps and water. Water was also tested as plasticizer. Other plasticizers that were tested were PEG400 and Acetyl triethylcitrate. Different batch sizes were tested (330 g, 400 g, 600 g and 1000 g of core beads). Proportions of formulation parts were varied (e.g. 57% core beads, 19% binder solution, 19% of coating polymer and 5% water; 51% core beads, 25% binder solution, 17% coating polymer and 7% water). Cellets 500 and CP-507 pellets were tested as core beads. Also the phases (different phases included in the process e.g. wetting with binder solution, wetting with water, drying, spheronization), duration of the phases (examples of total processing times: 48 min, 63 min, 67 min, 80 min, 86 min etc.) and settings of process were varied.

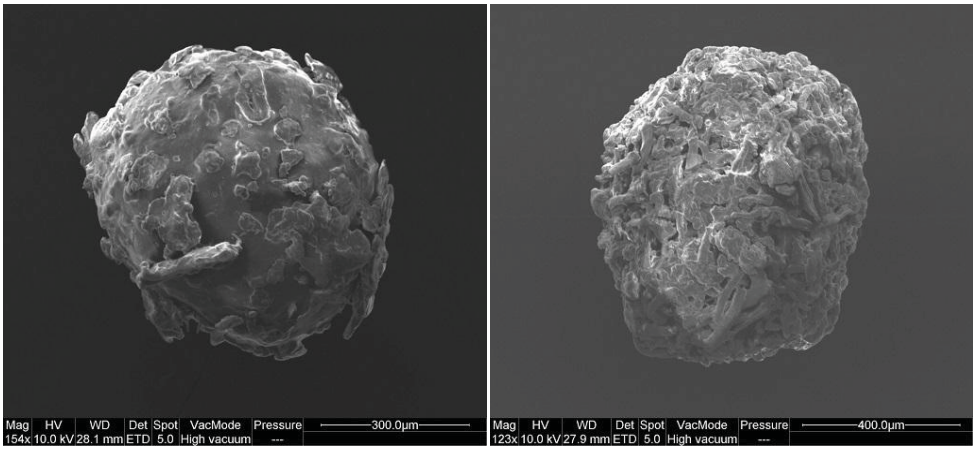
Effects of different liquid(s) used for wetting and plasticization were examined: Water was used for wetting and as a base for binder (or mixture of binder and plasticizer) solution for coating. Using the binder solution for the wetting was tried. Tests to remove the binder from the spray liquid mixture were also performed. The wetting time was varied to decrease the agglomeration. The amount of plasticizer compared to dry powder was varied.

The rotor speeds were varied between coating, spheronization and drying (150 - 300 rpm). The effect of rotor speed (when kept constant) to particle size distribution and sphericity was examined. The sphericity was slightly lower (0.87 v. 0.89) and the particle size distribution was approximately the same when the rotor speed was increased from 150 to 300 rpm. A separate drying phase was introduced and later combined with the

spheronization phase. The drying phase was removed and replaced with the spheronization phase of higher temperature. The effect of the spheronization time was examined.

No major differences in particle size were seen when coating polymer was changed from K100LV to K4M. No direct comparisons could be made when K15CR was changed to K100LV because the core type was changed at the same time. The granulated carbomer grade could not be coated on the CP-507 pellets. The fluidized bed collapsed due to electrostatical effects. The fine carbopol grade could not be processed into the rotor granulator because it did not come out from the screw feeder.

For batch 12092013 (Appendix 1: Figure I) only a binder liquid (6% HPMC 3cP) was used. This batch had a lower amount of binder compared to batch 11092013, higher coating (and drying) temperature, drying time and higher rotor speed. From SEM pictures it can be seen that there is not much coating on pellets of batch 12092013 (Figure 10). When the amount of binder liquid was increased from 200 g to 300 g and the coating temperature was lowered from 50°C to 30°C, the amount of coating increased (Figure 11). When water was used as the only plasticizer (for batch 18092013) an increased amount of agglomerates was observed. The span value of batch 18092013 is 0.73 and the Span value of batch 16092013 is 0.38(Appendix I). The significance of batch size was examined by increasing the amount of core beads from 600 g to 900 g. No significant differences were seen on particle sizes (also agglomeration) or on sphericities.



Figures 10 and 11. SEM pictures of pellets from batch 12092013 (left) and batch 16092013 (right).

8.2 Design of Experiments

Each of the parameters of the coating process is important but during the pre-experimenting only few parameters were selected and altered (amount and type of plasticizer, temperature, rotor speed, batch size). These parameters seemed to have a significant impact on measured results. Without a design of experiments it would be very time consuming and it would require deep insight and experience to find the optimal parameters for each new formulation (Antony J 2003). Produced pellets were characterized in different ways and the results were evaluated (Table 12).

Table 12. Results from all of the characterizations done for DOE pellets: friability (fri), loss on drying (LOD), Span, coating efficiency (CE), sphericity (sph), pycnometric density (pyc), bulk density (bulk), apparent density (app), porosity (por) and average pore diameter (avg)

	fri (%) n = 3	LOD (%) n = 1	Span n = 3	CE (%) n = 1	sph n = 3	pyc (g/cm^3) n = 4	bulk (g/cm^3) n = 1	app (g/cm^3) n = 1	por (%) n = 1	avg (µm) n = 1
DOE1	0.16	9.40	0.50	79.4	0.85	1.45	1.23	1.54	20.3	0.05
DOE2	0.55	4.74	0.43	91.8	0.88	1.45	1.24	1.53	18.7	0.05
DOE3	0.24	6.09	0.45	89.7	0.88	1.45	1.24	1.57	20.9	0.04
DOE4	0.08	2.60	0.78	86.0	0.87	1.46	1.21	1.53	20.8	0.04
DOE5	0.53	6.70	0.65	90.7	0.82	1.47	1.25	1.56	19.5	0.04
DOE6	0.89	2.12	0.61	90.8	0.82	1.44	1.18	1.51	21.9	0.05
DOE7	0.40	3.94	0.50	87.2	0.88	1.47	1.27	1.55	18.0	0.03
DOE8	0.42	9.52	0.41	98.3	0.89	1.44	1.27	1.59	20.0	0.06
DOE9	0.10	10.0	0.68	117	0.84	1.44	1.35	1.66	18.6	0.04
DOE10	0.15	5.50	0.66	93.9	0.84	1.45	1.18	1.52	22.0	0.06
DOE11.3	0.54	4.88	1.79	90.2	0.86	1.46	1.27	1.54	17.9	0.04
DOE12.2	0.98	10.4	2.44	83.6	0.86	1.44	1.24	1.56	20.6	0.06
DOE13	0.28	2.84	0.53	88.4	0.85	1.45	1.24	1.50	17.3	0.04
DOE14	0.09	4.56	0.58	92.0	0.88	1.45	1.22	1.54	20.9	0.04

DOE11 and DOE12 could not be measured representatively so their results were replaced with new batches DOE11.3 and DOE12.2.

8.3 Correlation

Correlation coefficient r (product-moment coefficient of correlation, Pearson's correlation) has a value between -1 and +1 (Wolfram Math World). Total positive correlation is +1, no correlation is 0 and total negative correlation is -1. A positive correlation is additive and a

negative correlation is decreasing. There are some strong correlations between the responses (Appendix 3). Response pairs that had a correlation coefficient with a higher absolute value than 0.5 are listed in Table 13. These correlations as well as the other moderate correlations in the table are discussed later in the text.

Table 13. Pearson's correlation and coefficient of determination response pairs that have highest correlation of the measured responses

Response 1	Response 2	Correlation coefficient	r^2
avg fria	span	0.558	0.311
LOD	bulk den	0.501	0.251
LOD	app den	0.700	0.490
CE (no water)	bulk den	0.634	0.401
CE (no water)	app den	0.732	0.536
avg pyc den	avg pore d	-0.606	0.367
bulk den	app den	0.852	0.725
bulk den	por	-0.689	0.474
por	avg pore d	0.676	0.458

8.4 Particle size distribution and sphericity

The particle size of the pellets is dependent on the coating level (more material on the cores can lead to higher diameter), core size (diameter), coating efficiency (increase of the amount of the material can lead to higher diameter) and the density of the coating (lower density leads to higher diameter if the amount of coating material remains the same) among other things. The diameter of the coated pellets is hard to predict before the DOE evolution because the amount of plasticizer and spheronization temperature vary from batch to batch. Sphericity increases during the spheronization phase.

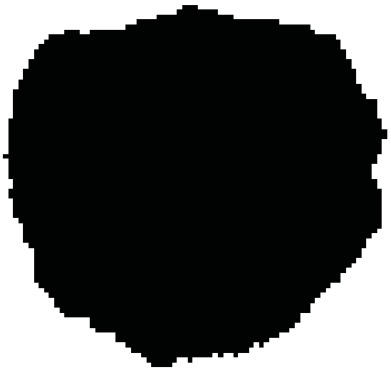


Figure 14. Vector image of pellet from batch 01102013 created by QicPic's software.

8.4.1 Particle size distribution

As a response from the DOE a particle size distribution value called Span [(x90 – x10)/x50] was used. The lower the deviation in the diameter of the pellets becomes the closer to 0 the Span value gets. In a real world situation the deviation of coating thickness can be set to a certain level; some micrometers or percents of optimal diameter.

The CP-507 core pellets had x50 value of 643 (± 7) µm and x90 – x10 was 180 µm, when analyzed with QicPic. The Span value of the CP-507 was therefore 0.28. The CP-507 pellet batch has a wide particle size distribution and furthermore is bimodal (Figure 15). The bimodality and wider particle size distribution is transitioned on to product pellets (Appendix 6). To make sure that these are batch characteristics, core material from another supplier (Cellets 500) was analyzed. The Span value of the Cellets 500 was 0.20.

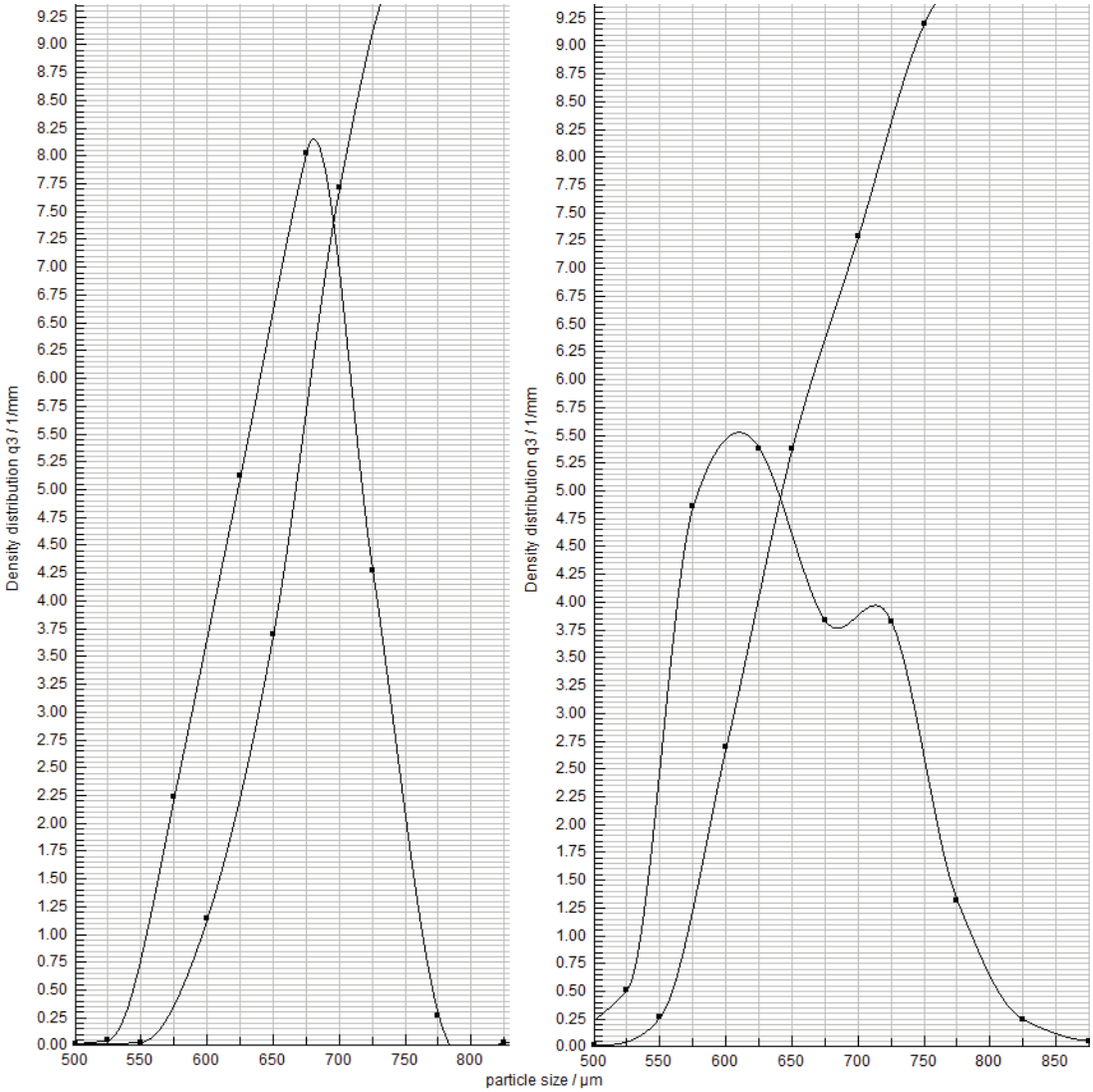


Figure 15. Density distribution – Particle diameter graphs of Cellets 500 (left) and CP-507 (right) core pellets. There is some peaking at 700 – 750 µm besides the main peak in the distribution curve of CP-507.

Wide particle size distribution and bimodality of the pellets can lead to segregation during the handling and coating of the pellets (Atarés et al. 2012). To prevent this, the core material can be sieved. However, during the experiments in the present work the samples were not sieved. To get representative samples the pellets for the coating were taken from the bottom of the product container.

Coating creates some deviation to the range of particle size, but the goal should be to minimize this deviation. The target x90 – x10 value and x50 value of coated pellets were also based on the same measurements of CP-507 core beads. The target x90 – x10 value was 180 µm (no increase to the width compared to the initial core beads). Target x50 value would be 643 + 2*n* µm, where *n* is wanted coating thickness. No actual value for *n* was evaluated from the data. These values (x90 – x10 and x50) should produce a Span value that is less than 0.3, because the x50 value is higher than for the CP-507 cores and the x90 – x10 value is the same if the coating thickness is assumed to be the same for small and large particles. On the other hand if the small and large particles are not coated to the same extent the value of x90 - x10 is hard to predict. Similar (to uncoated situation) value for x90 - x10 is most likely only achieved in a situation were the cores are of same size

The batch with the smallest Span value (DOE8) has similar distribution curve as core beads whereas the batch with highest Span value (DOE12.2) has a gentler curve compared to the other two (Figure 16). This indicates that a batch with small Span value has a coating that is equally thick on cores of different sizes and that the amount of agglomerates is small. A batch with high Span value on the other hand has a large amount of agglomerates. A batch with lowest coating efficiency (DOE1) and batch with a high coating efficiency (DOE9) have somewhat similar particle size distribution curves but their angle differ at the high end of cumulative distribution. This could suggest that the batch with higher coating efficiency has thicker coating and more agglomerates (Figure 17).

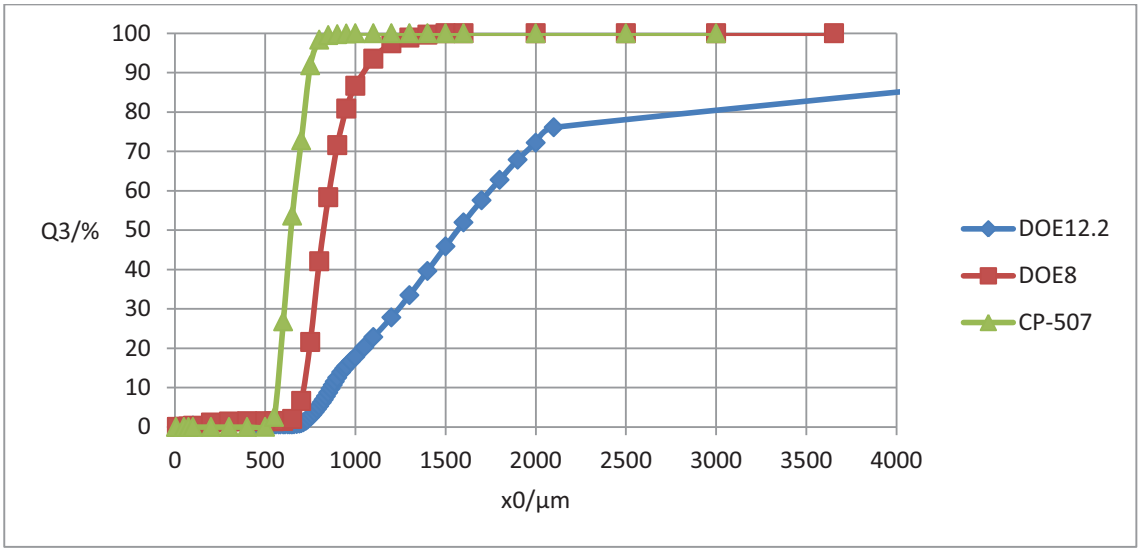


Figure 16. Cumulative distribution of batches with the smallest Span value (DOE8) and the largest Span value (DOE12.2) compared to cumulative distribution of core beads CP-507.

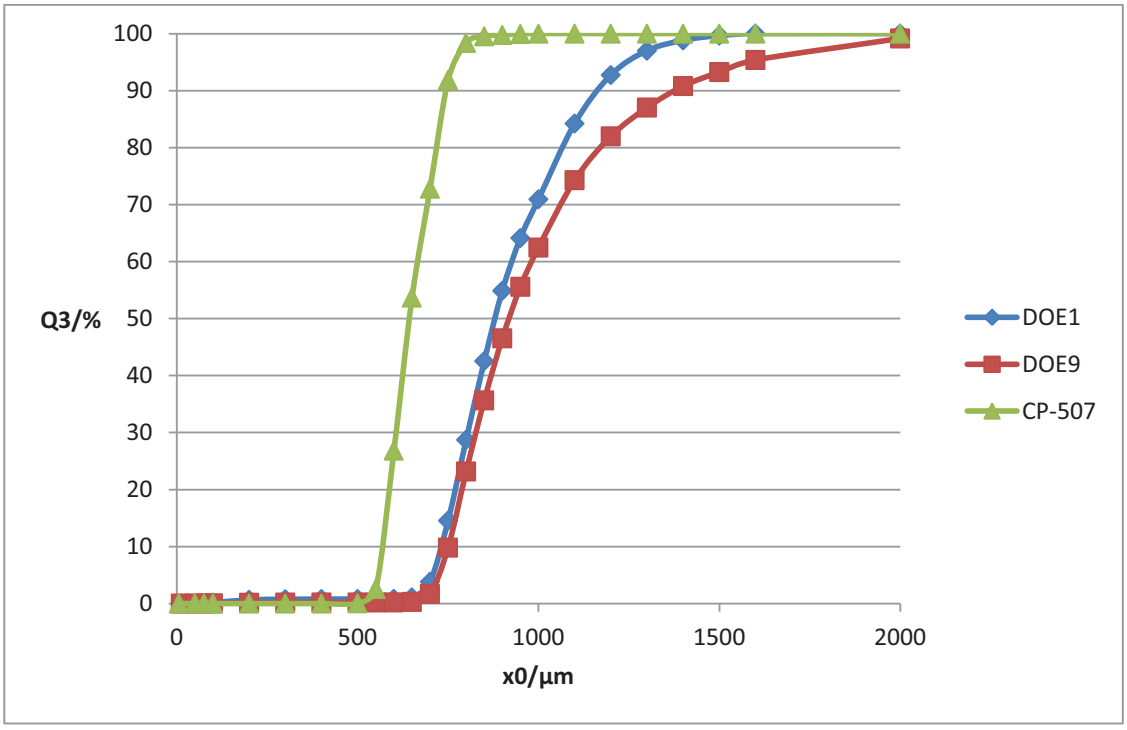


Figure 17. Cumulative distribution of the batch with lowest coating efficiency (DOE1) and highest coating efficiency (DOE9) compared to the cumulative distribution of core beads (CP-507).

Table 18. Mean particle size distribution of DOE batches

	x10 (µm) (n = 3)	x50 (µm) (n = 3)	x90 (µm) (n = 3)	x90-x10 (µm) (n = 3)	Span
Cellets 500	594	666	730	136	0.20
DOE1	729	881	1170	438	0.50
DOE2	689	811	1040	351	0.43
DOE3	698	814	1060	364	0.45
DOE4	680	862	1360	676	0.78
DOE5	718	940	1330	613	0.65
DOE6	724	940	1290	570	0.61
DOE7	653	768	1040	383	0.50
DOE8	712	824	1050	337	0.41
DOE9	750	920	1380	627	0.68
DOE10	738	912	1340	601	0.66
DOE11	763	1170	2290	1530	1.31
DOE11.3	834	1290	3130	2290	1.79
DOE12	501	2720	6310	5810	2.14
DOE12.2	897	1580	4750	3850	2.44
DOE13	701	842	1150	450	0.53
DOE14	707	855	1200	494	0.58

Batches DOE11, DOE12, DOE11.3 and DOE12.2 have mean and median Spans that are significantly higher than the values of other batches of the DOE. This most likely has an effect on the predictive abilities of the model for Particle Size Distribution. The mean value of the Span for all the experiments in the design was 0.90 and the median was 0.65. If batches DOE11.3 and DOE12.2 are excluded the mean value is 0.73 and median is 0.59. If batches DOE11 and DOE12 are excluded mean is 0.79 and median is 0.59. If all four batches are excluded mean is 0.57 and median is 0.56.

The lowest Span value, 0.41, was found for DOE8. This batch has the smallest x90 - x10 value and one of the smallest x50 values. DOE2, DOE3, DOE1 and DOE7 have the smallest Span values after DOE8. None of the batches reach the goal value of 0.3. This is most likely because the agglomeration increases both the x90 and the x50 values of most of

the batches. DOE1 has quite bimodal distribution (Appendix 6). Distributions of other batches (DOE2, DOE3, DOE7 and DOE8) are skewed to the right but they did not have that obvious bimodality.

Based on the Span values some outliers could be identified among the batches. Batches DOE11 and DOE12 had agglomerates that were too big to be analyzed by QicPic. Some of the agglomerates of DOE11 and DOE12 were around 10 centimeters in diameter (Figure 19). These batches had to be sieved. The outlet width of the QicPic equipment was changed to 10 mm and measurement range, gap and feed rate settings were also adjusted. The biggest agglomerates were produced because the batches had low rotor speed (100 rpm), high powder feed rates (11 g/min and 14 g/min) and high spray rates (22 g/min and 28 g/min) at the same time. There is also DOE4 with Span value of 0.784.

Figure 19. Comparison of batches with and without adjusted parameters. Scale in pictures is different.

The importance of these parameters (rotor speed, powder feed rate and spray rate) on coating level was evaluated by Kablitz and Urbanetz (2013) and confirmed by the extreme agglomeration in this design. Low rotor speed hinders distribution of liquid and mixing of the material (Dixit and Puthli 2009). This combined with high spray rate and wet mass created the unusually big agglomerates. In wet coating the properties of pellets and the coating efficiency are dependent on the mixing intensity (solid flow pattern) and water/moisture content present in the formulation (Ghebre-Selassie and Knoch 2002;

Bouffard 2007). A certain velocity of rotation is needed for the helicoidal flow pattern to be formed. Too low speed leads to lumping of the pellets and sticking to the walls. Too high speed leads to increased particle-particle and particle-wall contacts (collision velocity and frequency). This in turn leads to chaotic flow patterns and increased particle breakage. Decreasing air flow rate or gap air pressure also decreases the helical flow pattern.

Thus rotor speed was adjusted to 200 rpm for both batches (DOE11 and DOE12) and with these less extreme settings batches DOE11.3 and DOE12.2 were produced. As can be seen from the Figure 19, the agglomeration was less problematic with higher rotation values. This way better batches were produced and representative characterization was possible. On the other hand changing one parameter hinders the functionality of the definitive screening's fold-over structure.

From Table 18 can be seen that the original DOE11 and DOE12 have better Span values than their new versions DOE11.3 and DOE12.2. The better quality of batch DOE11.3 can be seen from x50 and x90 values, but for DOE12.2 these values are larger than the original's. DOE11.3. has large standard deviations for x10, x50 and x90 compared to DOE11 (Appendix 6). However, the results of DOE11 and DOE12 are unreliable, because of the sieving and the fact that biggest agglomerates didn't fit in the equipment.

The two-factor effect of the ratio between powder feed rate and spray rate and rotor speed seems to be the coefficient with most increasing effect on the size of Span (Appendix 5). This is due to the big agglomerates of DOE11.3 and DOE12.2 that were still quite big even after raising the rotor speed from 100 rpm to 200 rpm and can be seen as outliers 5 and 8 in observed vs. predicted –plot (Appendix 5). Most decreasing effect on Span comes from the rotor speed and the amount of plasticizer. The batches with high rotor speed and high plasticizer percent had a less wide PSD. Other coefficients that did have effect on Span were main effects powder feed rate and ratio between powder feed rate and spray rate and the two-factor effect of plasticizer amount and powder feed rate. Increasing powder feed rate increased the width of PSD (at least when combined with low rotor speed) and

combined with low amount of plasticizer in the formulation the effect was increased. Increasing spray rate compared to powder feed rate decreased the width of the PSD. These coefficients seem to be on-the-line with previous observations and the basic theory of fluidized bed rotor granulation.

8.4.2 Sphericity

Sphericity was chosen as a good shape value for pellets, since a uniform coating should result in more spherical pellets. CP-507 pellets have a sphericity value of 0.92 (x50). This is also the target sphericity. If the spheronization phase is successful, higher sphericity values may also be possible. There is not much difference of sphericity between CP-507 and Cellets 500 core beads (0.92 v. 0.93). Sphericity values of the DOE batches and the core beads are presented on Appendix 7 and Table 12. Noticeable, though not surprising, is that all batches are less spherical than the core beads.

Most variation in sphericity is seen at the lowest part of density distribution (x10) where sphericity varies from 0.71 to 0.85. x50 and mean (x10, x50 and x90) sphericity values of all batches have almost or completely the same mean and median values and standard deviation is only 0.02 for both values. The variation of x90 values is also minimal. Good sphericity values indicate that the spheronization phase works well or that the coating phase produces round pellets even before spheronization and the spheronization phase does not make the situation significantly worse. From PSD values it can be seen that there are some agglomerates in all batches. Apparently the agglomerates are also quite spherical.

Excluding DOE1, the batches with smallest Span values also have the lowest average sphericity values. Agglomeration lowers the sphericity (DOE12) and a low coating level could lead to higher sphericity. Batches DOE5 and DOE6 could be named as outliers with their low average sphericity of 0.81.

To follow the development of sphericity during batch manufacturing an experiment was run where samples were taken during the wetting, coating and spheronization phases. The sphericity and morphology of these samples were examined (Figure 20, Figure 21).

Not much significant information can be gained from sphericity values for the optimization of coating parameters because the differences are small and thus the model does not work well. On the other hand this shows that the manufacturing method is robust with regards to sphericity. The model with average sphericity worked even worse than the model with x50 values. Other shape values and measurement methods could be tested to obtain more discriminating values.

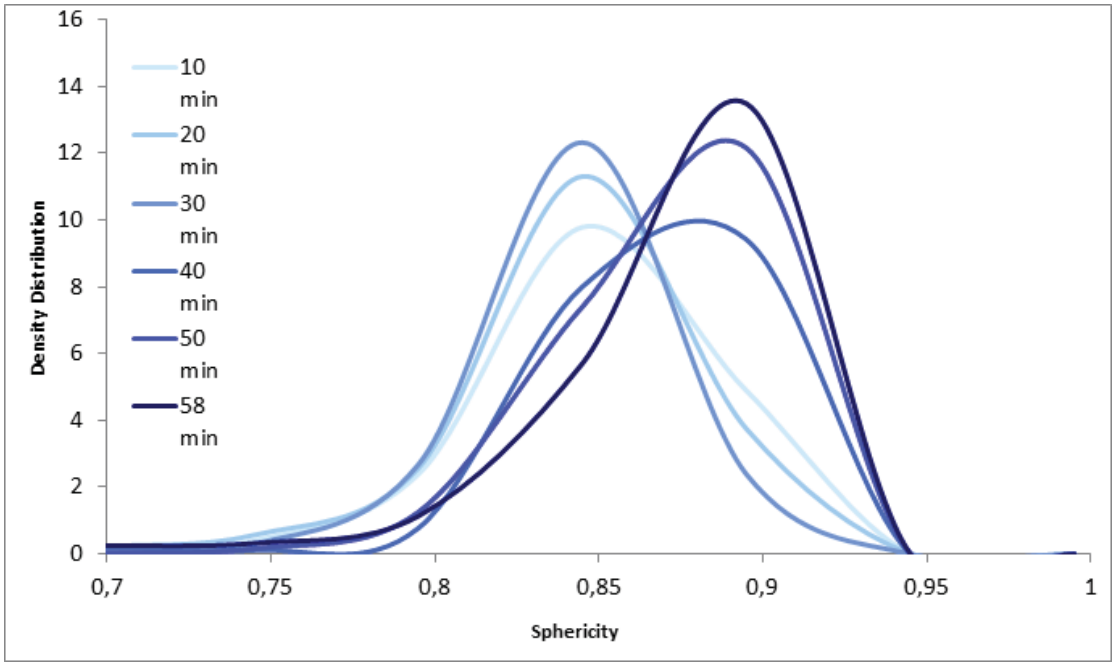


Figure 20. Sphericity changes during coating and spheronization. Coating lasted 40 minutes and spheronization lasted 20 minutes.

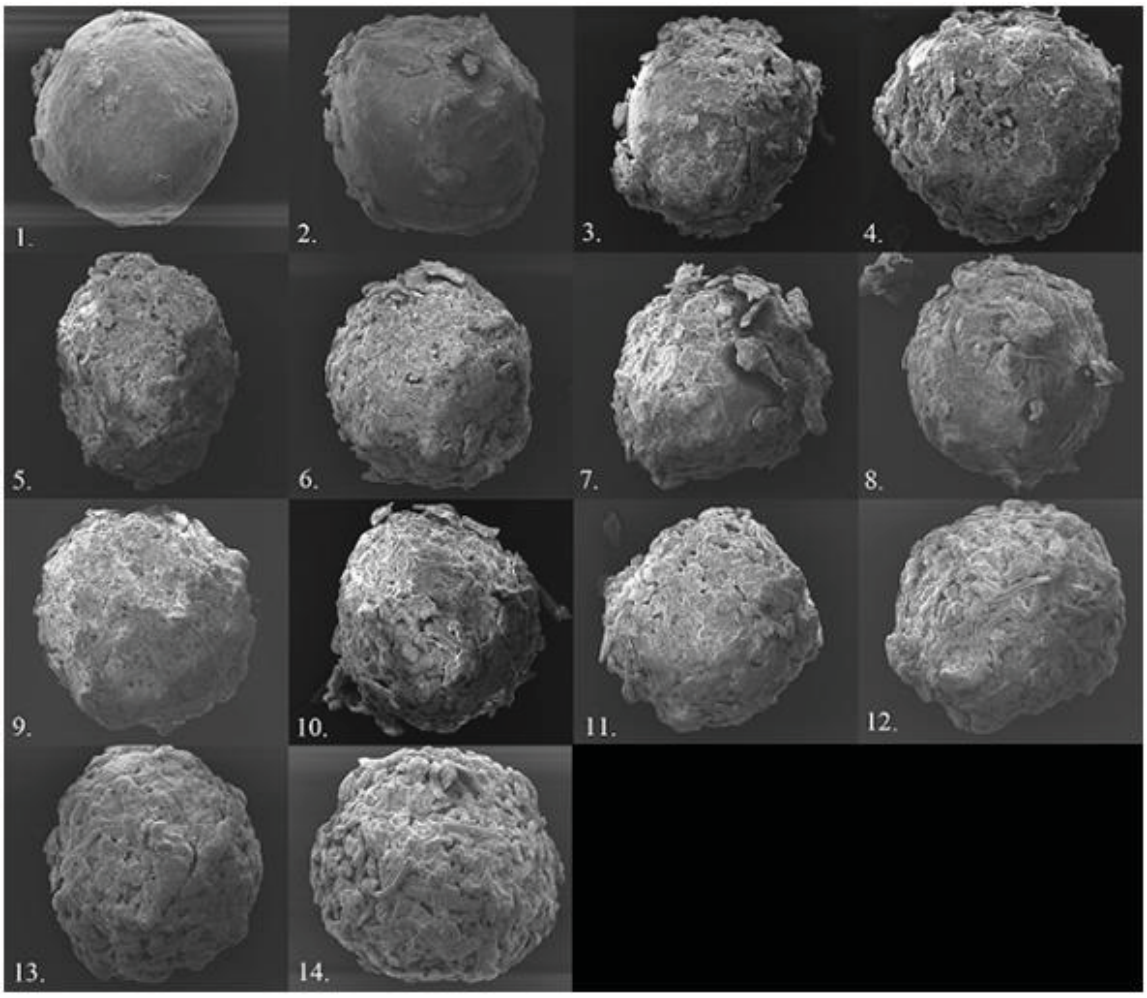


Figure 21. SEM pictures of sample pellets taken during one coating at different time points. Wetting phase was 1 minute, coating phase about 50 minutes and spheronization 20 minutes.

8.5 Morphology and shape

It can be observed that design settings produced heterogeneously coated pellets. Surface pictures were taken of randomly chosen pellet per batch: whole pellet, close-up of the surface and after curing at 80°C in oven (Figures 22, 23 and 25). Some pellets were halved before the gold coating for cross-section figure (Figure 24).

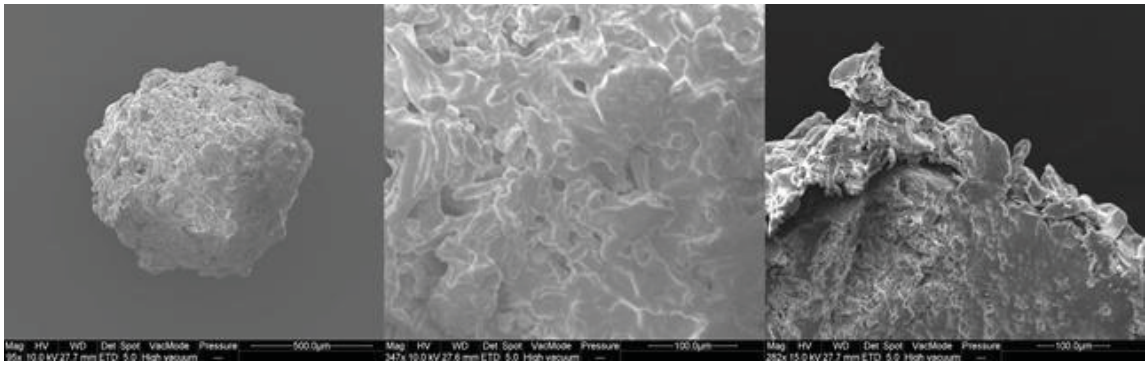


Figure 22. SEM pictures of DOE1: whole pellet, pellet surface and cross-section (two different pellets from the same batch).

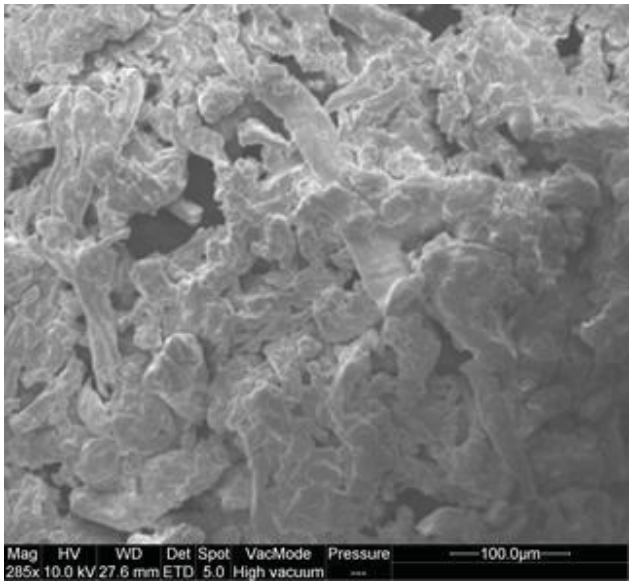


Figure 23. Surface of a DOE2 pellet: separate polymers and holes visible.

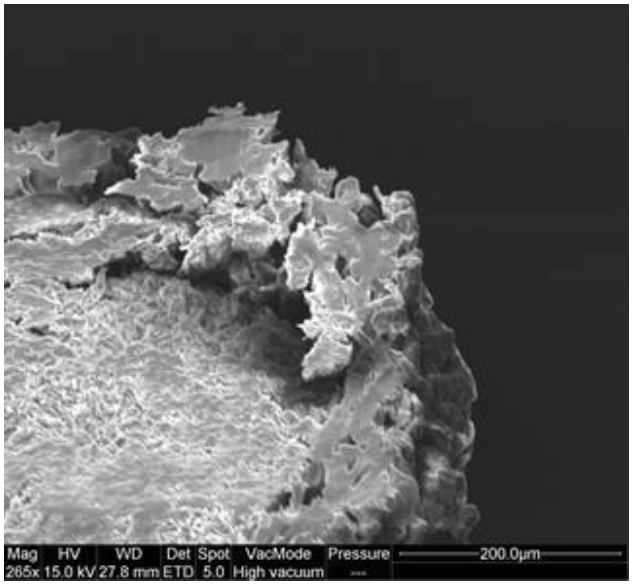


Figure 24. Cross-section of DOE2 pellet: core and coating.

In close-up pictures and cross-section pictures it can be seen that the coating is uneven and there are holes of different sizes unevenly distributed throughout the coating (Figure 23; Figure 24). This would indicate that the erosion of polymer layer will most likely not be systematic or controlled. Those parts of the coating that do not have holes look denser and less porous than the core bead. This could have been caused by the cross-sectioning method (surgical knife). To improve the coating quality, higher spheronization temperatures and higher plasticizer amounts should be used. It is also possible that the plasticizer had a too high contact angle with the coating polymer and it did not lower the T_g enough. The plasticizer might not be sufficiently mixed with the coating polymer and does not enter sufficiently into the coating polymers.

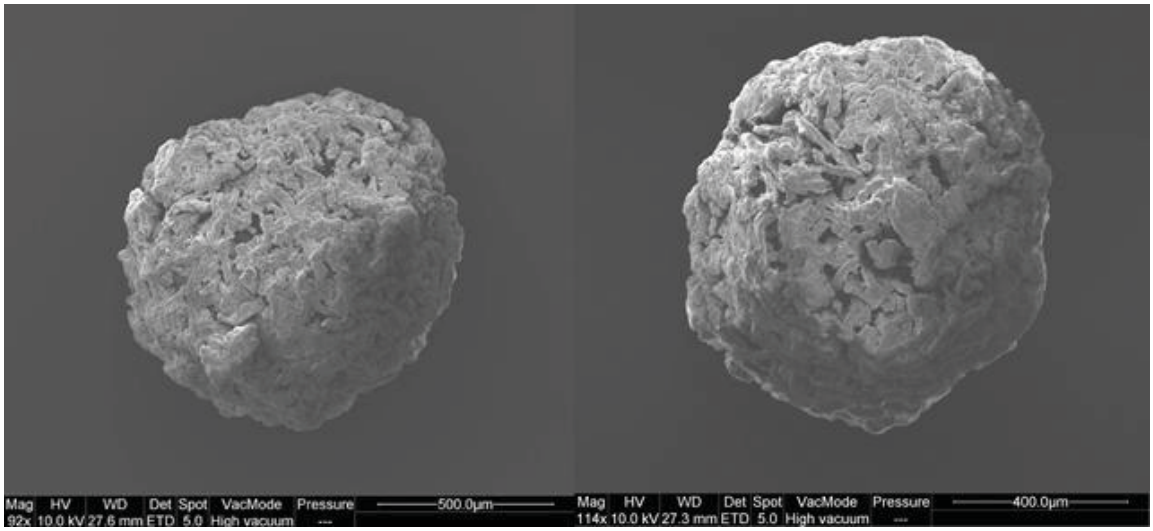


Figure 25. Pellets from batch DOE2: before (left) and after (right) 24 h curing in oven at 80°C.

Comparing pellets of Figure 25 it can be seen, that no great difference is caused by curing at 80°C to this batch. This indicates that T_g of the coating was not lowered enough. During the curing process in an oven on trays the pellets are immobile and heating is not homogeneous from all directions to pellet. This can also create error in the results. But as no significant differences can be seen in the SEM pictures, it can be said that curing at 80°C did not have significant visual effect on the coating structure. Higher curing temperatures should have been tried also (e.g. 100°C and 120°C).

In close-up pictures uncoalesced polymers can be recognized on the surface of pellets and there are large holes on the coating both without and with oven curing (Figures 25, 26 and 27). None of the batches showed complete film formation, but in some batches slight film formation can be seen e.g. DOE9 and DOE13 (Figure 27).

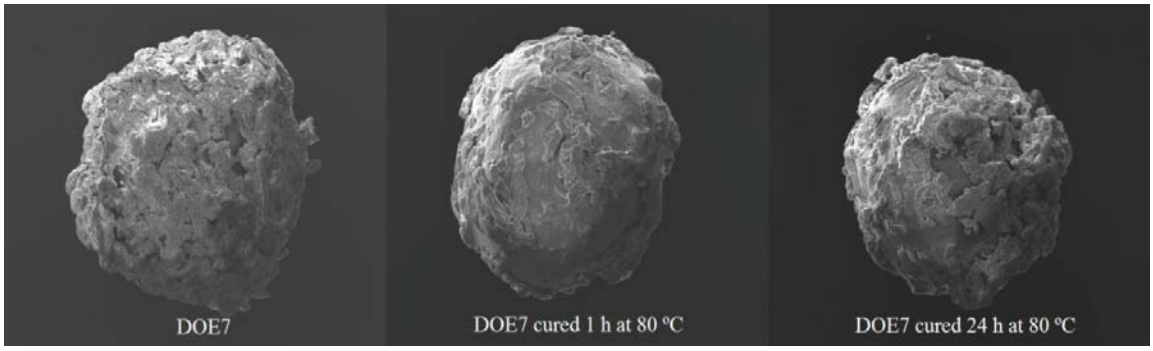


Figure 26. Three different pellets from DOE7 batch: “normal”, cured 1 h at 80ºC and cured 24 h at 80ºC

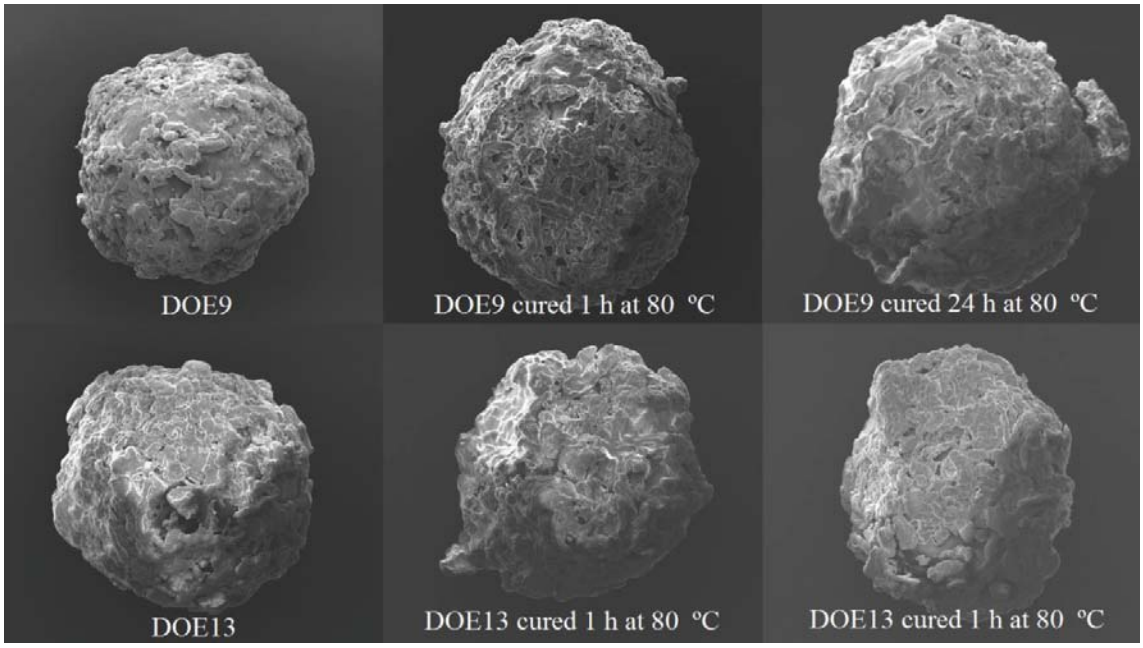


Figure 27. Three different pellets from batches DOE9 and DOE13

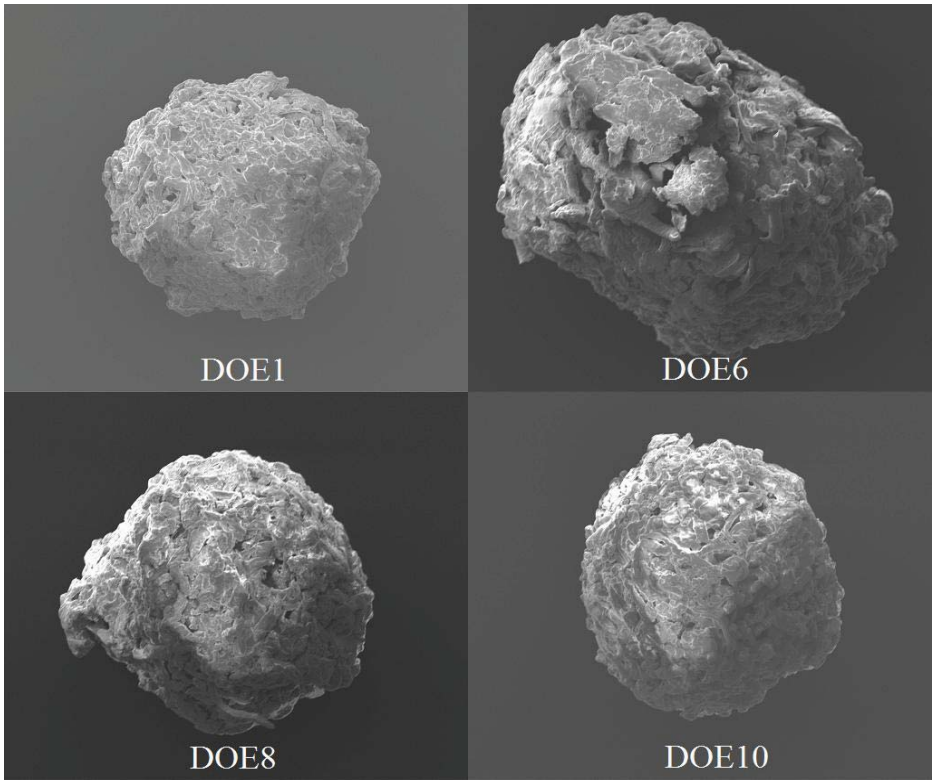


Figure 28. Pellets from batches DOE1, DOE6, DOE8 and DOE10

8.6 Erosion

The erosion rate was examined using the USP paddle method and SEC-MALS size exclusion chromatography to determine the HPMC concentration in the dissolution liquid. Only samples from DOE1, DOE2, DOE7 and DOE8 were analyzed. From these samples it can be concluded that this method is applicable for characterization of erosion rates. This method can also be used to measure coating efficiency because it measures the amount of released HPMC from coating.

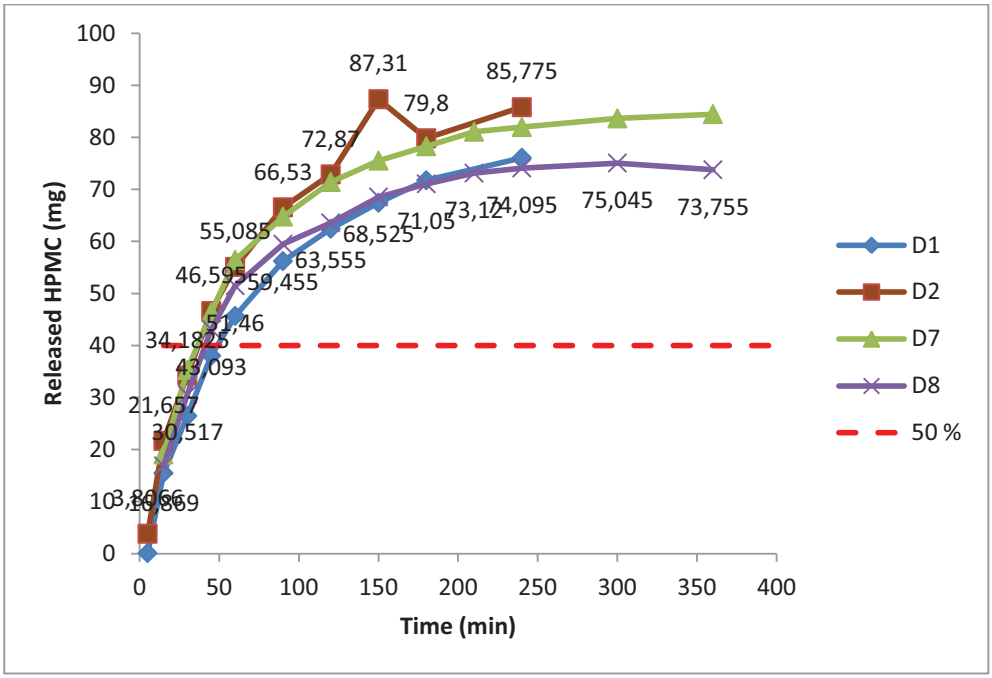


Figure 29. Total weight of the released HPMC from coated pellets calculated based on the concentration of SEC samples

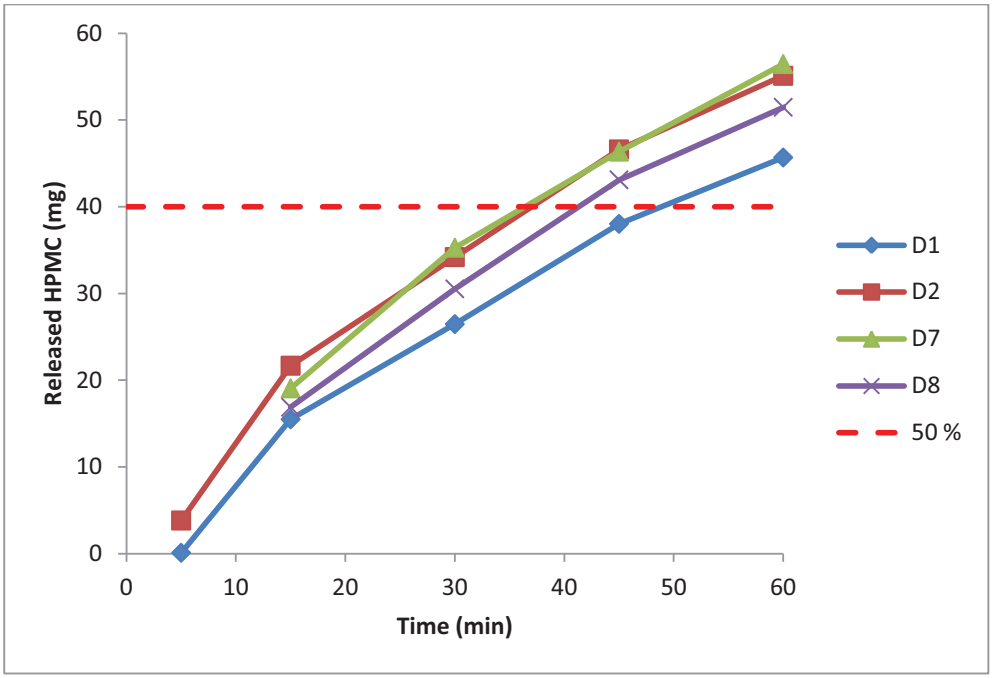


Figure 30. Weight of the released HPMC from coated pellets during the first hour

The release rate of HPMC decreased when 75 - 85 mg had been released from the 500 mg sample. The coating efficiencies based on these measurements are roughly 63% for DOE1, 73 % for DOE2, 59% for DOE7 and 73% for DOE8.

The coating efficiencies based on released amounts of HPMC don't correlate completely with coating efficiencies based on weight but there are some similarities (Table 31). This indicates that erosion method could be possibly used to predict the erosion rate of the coating and other useful information could be derived from this data to optimize the coating process. Some differences can be seen in the release rates (mg/min) of coated DOE pellets (Figure 30) but the slopes are mainly quite similar. It is possible that the differences are related to the coating structure of pellets, because the batches with lower apparent density have higher release rate. On the other hand pycnometric density and average pore size do not support this.

The experimental error of the method seems to be minimal (Appendix 8). Standard deviations are very small with only one larger deviation which seems to be related to a measurement error. More batches should be examined to make a more sound decision about the reliability of the dissolution and SEC-MALS method.

Table 31. The summary of coating efficiency based on erosion CE (e), Coating efficiency (without water) (CE), Loss on drying (LOD), Pycnometric density (pyc), Apparent density (app) and Average pore diameter (avg) of batches DOE1, DOE2, DOE7 and DOE8.

Batch	CE (e) (%)	CE (%) (n = 1)	LOD (%) (n = 1)	pyc (g/cm^3) (n = 1)	app (g/cm^3) (n = 1)	avg (μm) (n = 1)
DOE1	63	79.4	9.40	1.45	1.58	0.05
DOE2	73	91.8	4.74	1.45	1.54	0.05
DOE7	59	87.2	3.94	1.47	1.55	0.03
DOE8	73	98.3	9.52	1.44	1.59	0.06

Dissolution measurements do indicate that some of the coating material was lost during the coating process in all batches. This was first observed after completed coating and opening the coating vessel where some of the coating powder was lost by sticking to container walls and by not adhering to the pellets.

8.7 Friability

Friability values for the batches vary from 0.08% to 0.98% (Appendix 9). There is about 10% difference between mean and median values. The mean standard deviation is 0.08%. Friability of CP-507 core beads was 0.01% with standard deviation of 0.01%. The acceptable weight loss during friability testing of tablets is 1% (USP). No pharmacopoeial (or other official) friability methods or requirements for friability of pellets is available. With this current method no friability was observed and this was also the goal for the coated pellets. Samples were not weighed after the fluidization process and there is no

knowledge how much of the abrased material builds up into the bottle. The friability figures can be compared to each other to determine the best parameters to create a durable pellet.

With original settings (DOE11 and DOE12 produced with 100 rpm rotor speed) there are only weak correlations with other results (Appendix 3). With adjusted settings there's a correlation (0.5578) between friability and Span value of batches. This could indicate that with larger coating level or larger range of particle size distribution friability is higher. Batches DOE6 and DOE12.2 could be named as outliers because of their high friability (Appendix 9).

Friability has great importance if API is included in the coating or the coating works as sub-coating for an API coating. Abrased material leads to inaccurate dosing. Changing the friability method could give different kind of results. If the friability method had been less product-consuming (now the method required three 100 g samples of every batch) different parameter settings of the friability method could have been tried.

8.8 Loss on drying and Coating efficiency

Loss on drying values vary from 2.1% to 10.4% among the DOE batches (Table 32). LOD values for CP-507 core beads and HPMC K4M powder were 2.4% and 4.1% respectively. LOD of PEG 400 was 1% (literature value). If no water is bound to the coating and it is assumed that PEG400 does not affect LOD value, the LOD for coated pellet (with 100% coating efficiency) would be 2.8% (2.4 x 0.75 + 4.1 x 0.25 = 2.825). If PEG 400 is taken in this equation the LOD is (2.4 x 0.75 + 4.1 x 0.2475 + 1.0 x 0.0025 = 2.817) or (2.4 x 0.75 + 4.1 x 0.175 + 1.0 x 0.075 = 2.593). This means that in some batches (DOE4, DOE6 and DOE13) almost all water has evaporated during spheronization (Table 32). CE was also calculated so that the whole LOD was deducted (by deducting the individual LOD values of the excipients from the starting material). Even these values do not tell the actual coating efficiency because the loose powder was also included when the final product was

weighted though these amounts could be minimal. Unfortunately no accurate weightings of the percentage of the loose powder were made.

In the yield valculation the core beads are included but otherwise the calculation is the same as for CE. Yield values are less than 100% (except for DOE9) when the LOD is deducted.This suggests that some of the powder is lost during the coating process. The yield values are also distorted by the weighing of the loose powder of the samples.

Table 32. LOD and CE values of batches

	LOD %	CE with H_2O	CE no H_2O	Yield with H_2O	Yield no H_2O
DOE1	9.4	120	79.4	106	93.8
DOE2	4.74	99	91.8	100	97.5
DOE3	6.09	101	89.7	100	96.9
DOE4	2.6	85	86.0	96	96.5
DOE5	6.7	107	90.7	102	97.7
DOE6	2.12	89	90.8	97	97.2
DOE7	3.94	92	87.2	98	96.8
DOE8	9.52	123	98.3	107	99.5
DOE9	10	150	117	112	104
DOE10	5.5	104	93.9	101	98.3
DOE11	6.25	99	99.4	100	99.8
DOE11.3	4.88	99	90.2	100	97.6
DOE12	9.4	120	98.4	106	98.4
DOE12.2	10.39	112	95.5	104	95.5
DOE13	2.84	89	96.8	97	96.8
DOE14	4.56	99	97.8	100	97.8

Pearson's correlation between LOD and CE (with water) is 0.914 with original settings (with DOE11 and DOE12 in the model) and 0.875 with adjusted settings (with DOE11.3 and DOE12.2 in the model). Similarities between LOD and CE values are most likely result of bound water in the coating because without water the correlation values are 0.329 and 0.222 for unadjusted and adjusted respectively. Overall there is little or no motivation to use the CE (with water) value if LOD is measured and dry CE value can be calculated. When CE value (with water) is over 100%, there is some water bound in the coating as a result of insufficient drying during the spheronization.

Weighed material included the loose powder that had not adhered on the surface of the pellets. Also the possible agglomerates were weighed with the product. By visual examination and sieving smaller amounts of the batch it could be seen that these amounts of free powder were small. These observations could be affected by segregation during storing and handling of the samples. In cases where CE (with water and without water) is less than 100% it is very likely that some of the powder has been lost. A constant (low) LOD could probably be achieved by spheronization at high temperature but this could cause other problems (e.g. sticking of plasticized material).

Some loss of coating polymer happens through the top filter of the equipment air ventilation. Powder also sticks to the expansion chamber walls and piles up in the filtration system. The loss is usually caused by inefficient wetting of core beads. On the other hand too high spray rate and/or insufficient drying leads to accumulation of water into the coating (Table 33). The quality of the coating should be checked from other characterization results even if the CE is high and LOD is close to the excipient values. These other sources can be for example density, particle size distribution, shape and SEM pictures.

Table 33. LOD values compared to spheronization temperatures and spray rates.

Batch	Temp (°C)	Powder feed rate (g/min)	Spray rate (g/min)	Batch size (g)	LOD (%)	x50 (µm)
DOE1	55	14	14	1000	9.4	880
DOE2	80	14	28	750	4.7	810
DOE3	30	11	11	500	6.1	810
DOE4	80	14	14	500	2.6	860
DOE5	30	8	11	750	6.7	940
DOE6	80	8	11	500	2.1	940
DOE7	55	8	16	500	3.9	770
DOE8	30	8	16	1000	9.5	820
DOE9	30	14	19	1000	10	920
DOE10	55	11	15	750	5.5	910
DOE11	80	11	22	1000	6.3	1200
DOE11.3	80	11	22	1000	4.9	1300
DOE12	30	14	28	500	9.4	2700
DOE12.2	30	14	28	500	10	1600
DOE13	80	8	8	1000	2.8	840
DOE14	55	11	15	750	4.6	860

There is some weak correlation between LOD and densities (Table 13). CE (without water) also has some weak correlation with all the three density values (stronger with apparent density). There are different possible explanations for these correlations. One is that when LOD and CE (with water) are high there is water bound in the coating and water is heavier and denser than the coating polymer. Other explanation is that bound water has plasticized the coating polymer and the coating is denser because of this. This was the goal of plasticization but it is not supported by the SEM pictures (Figure 28). Correlation between CE and average pycnometric density is negative and this indicates that higher coating level leads to lower density. This could be because the coating is less dense than the core bead.

Coating efficiency should have been measured of sieved products. After sieving the loss on drying should have been measured because it is possible that the loose powder contains more bound water than the coating of the pellets.

8.9 Density and porosity

From SEM pictures of produced pellets it can be seen that the coating of all of the batches is quite porous (Figure 22-28). Some batches have coatings, through which the core bead can be seen. Some coatings look partly solid and some look like there's mainly separate polymer particles stuck to the core. Curing the pellets at 80°C did not have a major effect on the pycnometric densities of DOE batches, and there seems to be no correlation to the original spheronization temperature (Appendix 10). Density and porosity of the coated pellets are compared with uncoated CP-507 core beads (Table 34).

Table 34. Densities measured with helium pycnometer and mercury porosimeter. Porosity and average pore diameters are measured with mercury porosimeter. Pycnometric density (pyc), bulk density (bulk), apparent density (app), porosity (por) and average pore diameter (avgpd)

	pyc (g/cm^3) n = 4	bulk (g/cm^3) n = 1	app (g/cm^3) n = 1	por (%) n = 1	avgpd (μm) n = 1
CP-507	1.50	1.46	1.58	7.23	0.016
DOE1	1.45	1.23	1.54	20.3	0.053
DOE2	1.45	1.24	1.53	18.7	0.049
DOE3	1.45	1.24	1.57	20.9	0.045
DOE4	1.46	1.21	1.53	20.8	0.044
DOE5	1.47	1.25	1.56	19.5	0.044
DOE6	1.44	1.18	1.51	21.9	0.052
DOE7	1.47	1.27	1.55	18.0	0.032
DOE8	1.44	1.27	1.59	20.0	0.058
DOE9	1.44	1.35	1.66	18.6	0.039
DOE10	1.45	1.18	1.52	22.0	0.055
DOE11	1.46	-	-	-	-
DOE11.3	1.46	1.27	1.55	17.9	0.037
DOE12	1.44	-	-	-	-
DOE12.2	1.44	1.24	1.56	20.6	0.055
DOE13	1.45	1.24	1.50	17.4	0.039
DOE14	1.45	1.22	1.54	20.9	0.042
mean	1.45	1.24	1.55	19.8	0.046
median	1.45	1.24	1.54	20.1	0.044
SD	0.01	0.04	0.04	1.4	0.007
min	1.44	1.18	1.50	17.4	0.032
max	1.47	1.35	1.66	22.0	0.058

Core beads have an average pycnometric density of 1.50 g/cm^3. This is clearly higher than the highest pycnometric density (DOE7 with 1.47 g/cm^3) of the coated pellets. The lowest measured pycnometric density is 1.44 g/cm^3 (DOE8). Same kind of difference between core beads and coated pellets can be seen for the bulk density, that is measured with mercury porosimeter. Mercury porosimeter also measured apparent density, porosity and average pore diameter. Core beads have bulk density of 1.46 g/cm^3 and the batch with the highest value is DOE9 with a bulk density of 1.35 g/cm^3. Apparent density of the core beads is 1.58 g/cm^3. Batches DOE8 and DOE9 have higher density than core beads. The mean apparent density (1.55 g/cm^3) is also quite close to the value of core beads.

There is no correlation between the density values measured with helium pycnometer and mercury porosimeter (Appendix 3). Pearson's correlation value between average pycnometric density and bulk density is 0.0212 and -0.1982 (weak negative correlation) between average pycnometric density and apparent density (Figure 35 and Figure 37). There is Pearson's correlation of 0.852 between apparent density and bulk density (Figure 36). Pycnometric density shows some correlation with average pore diameter. Bulk density has correlation with porosity. Density values have correlation with LOD and CE (without water) values as was mentioned in previously.

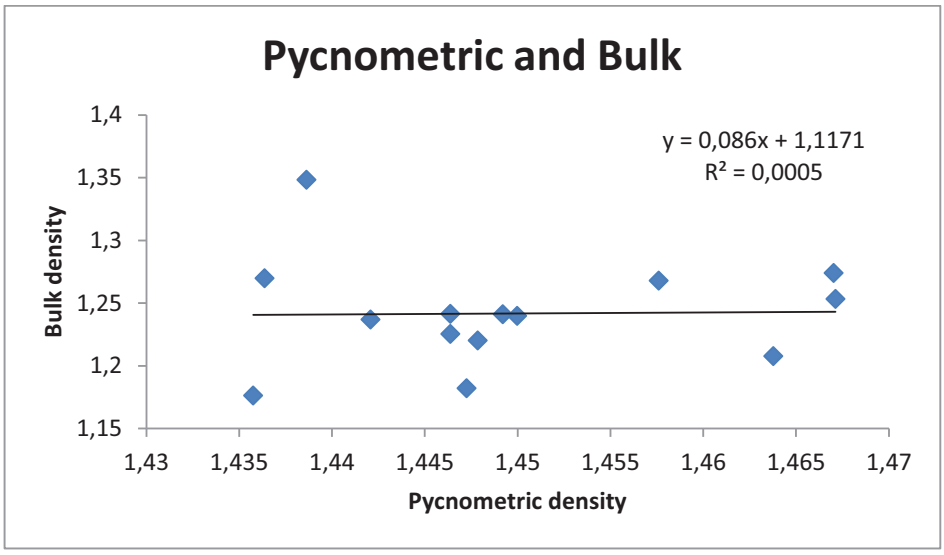


Figure 35. Correlation between Pycnometric density and Bulk density

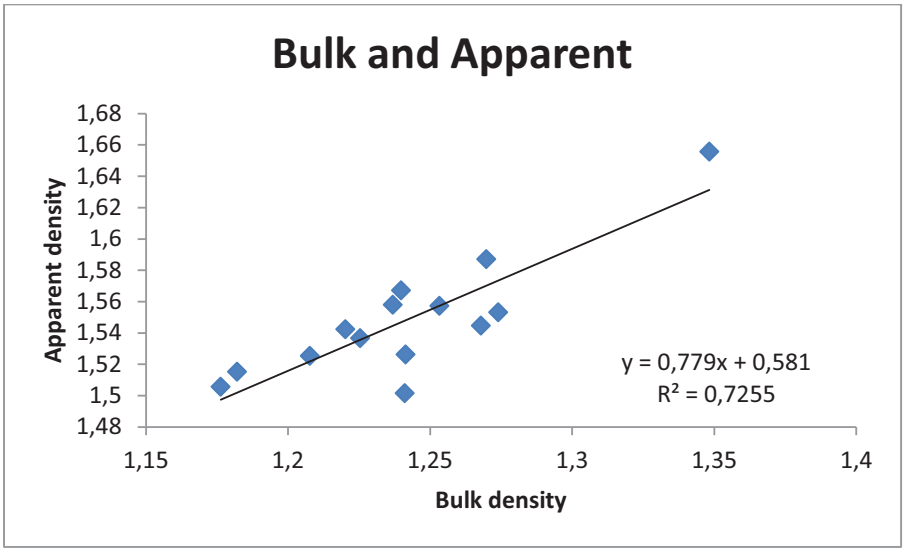


Figure 36. Correlation between Bulk density and Apparent density

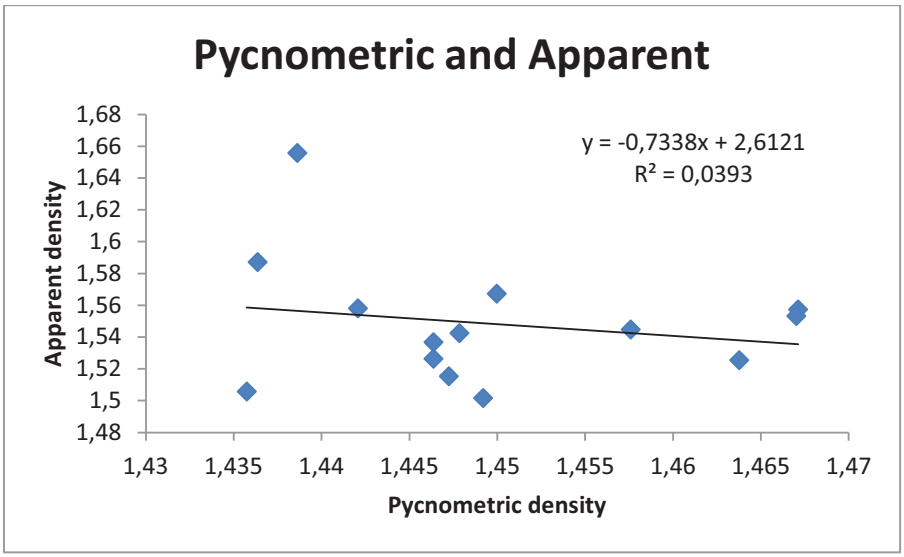


Figure 37. Correlation between Pycnometric density and Apparent density

DOE9 is an outlier for bulk and apparent density values and if it is removed from the calculation the correlation between bulk density and apparent density decreases to 0.667. Correlation between bulk density and porosity increases from -0.689 to -0.766.

Coated pellets have larger mean pore sizes and larger porosity than the core beads (Table 35). Thus it can be concluded that the higher coating level is the larger the mean pore diameter is when the coating is as porous as on the coated DOE pellets. There is a correlation of 0.676 between porosity and the average pore diameter. For the DOE batches the mean value of average pore diameter is 0.046 μm (Table 34). Batches DOE7 and DOE 11.3 have average pore diameter that is smaller than mean – SD; 0.038. These batches also have low porosity. DOE13 has similar values. In SEM pictures of DOE7 it can be seen that the core is partly visible through the coating (Figure 26). This indicates that the pellets of DOE7 have only a small amount of coating on them. As stated before the main factors affecting Span are the two-factor coefficient of the ratio between powder feed rate and spray rate and rotor speed. DOE7 has both high ratio (1) and high rotor speed (500 rpm). These could be the reasons for low amount of coating of this batch.

Batches DOE 9 and DOE13 have average pore diameters of 0.039 μm. These batches have very interesting looking morphology in the SEM pictures (Figure 27). In one picture of DOE9 it seems that the core is clearly visible, but in the other two pictures there seems to be a more even coating that is in some parts more dense looking. These two pictures are after curing, which might have affected the results (by increasing the temperature over the T_g), although not much evidence points in this direction. In the pictures of DOE13 parts of an even coating can be seen. In one of the pictures there might be core partly visible, but otherwise the coating seems even and without big gaps or pores. So the average pore size can be small, because the coating is only partly successful and the core is visible or the coating is actually dense and has small pores.

Batches DOE1, DOE 6, DOE8, DOE10 and DOE12.2 have the largest average pore size values (DOE8 and DOE12.2 have values that deviate from the mean more than SD). From the SEM pictures of batches it can be seen that these are a heterogeneous group of coatings (Figure 28). All batches have porous coatings. In one picture of DOE8 and one picture of DOE10 there might be core bead partly visible.

DOE8 has curious results as the average density value with pycnometer was much lower than in other batches and it deviates more than SD from the mean (Appendix 10). Measurements of DOE8 were repeated with pycnometer, but even though the average density increased slightly it still deviated more than SD from the mean. The second measurements of DOE8 gave densities that were at the same level with batch DOE6.

When the densities were measured with mercury porosimeter, DOE6 was still at the low end of density, but DOE8 had higher apparent density than the core beads (Table 34). Of all the batches only DOE 9 had higher apparent density than DOE8. As mentioned before DOE9 has one SEM picture where the core bead is clearly visible and two pictures where the coating is even and there is some film formation. These unordinary density values of DOE8 and DOE9 could be related to the unordinary LOD and CE values the batches have and to the drifting fluid flow during coating.

8.10 Models

Summary of Fit table is a visual presentation of the functionality of the models (Figure 38). Values that are included in the Summary of Fit table are R2, Q2, Model Validity and Reproducibility. Same values for the models are presented in numerical form in Table 39. R2 is coefficient of determination and it indicates how well the data points fit in a statistical model. R2 represents the percent of data that's closest to the best fit line. If R2 is less than 0.5 the model has low significance. Q2 means cross-validated R2 and it's been used to estimate model's robustness and predictive ability (Golbraikh and Tropsha 2002). It can be used to determine how certain the predictions of the model are. Significant model has Q2 value that’s more than 0.1 and good model has Q2 value that’s greater than 0.5. Model validity is a test of diverse model problems. Model’s validity value should be more than 0.25. Otherwise the model is not statistically significant. Reproducibility value is calculated by comparing variation between replicates to overall variation. Reproducibility should be greater than 0.5. Models were fitted with multiple linear regression technique. MLR fits the linear equation to observed data and predicts outcome of response variable.

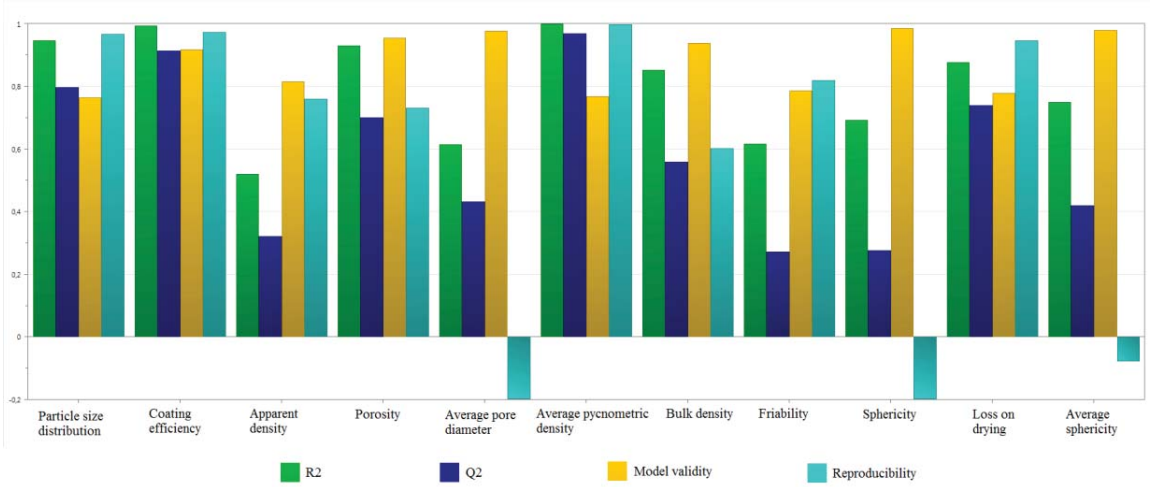


Figure 38. Summary of Fit table for models fitted with multiple linear regression (MLR): R2 (green), Q2 (dark blue), Model Validity (yellow) and Reproducibility (light blue).

The models rely on definitive screening's self-fold over system. This is problematic in situation where there are outliers in the results but the outliers cannot be excluded because the model needs all the results to function properly. If outliers are left to the result, the predictions made by the model are not reliable. Batches DOE11 and DOE12 had extreme settings of rotor speed and produced agglomerates that couldn't be tested with characterization methods. To be able to analyze the samples new batches were produced and rotor speed was moved from extreme setting of 100 rpm to 200 rpm. New settings made it possible to analyze representative samples from batches but at the same time they hinder functionality of the models, because the rotor speed settings are not at extreme point.

The choice between unrepresentative sample and hindered model has to be made. If outliers are left to the model, the results of the models have to be viewed in the light of the distorted results. If new adjusted settings are used it has to be taken to account by viewing the functionality of models in this light. Table 39 presents the differences between models with original settings and with unrepresentative results for DOE11 and DOE12 and the models with adjusted settings and representatively measured results. Adjusted settings give better models for pycnometric density, particle size distribution and coating efficiency (without

water). Original settings give better models for friability and loss on drying. Models have different factors which is seen from the coefficient pictures (Appendix 5) and condition numbers (Table 39).

Table 39. Summary of key properties of the models: coefficient of determination (R2), cross-validated coefficient of determination (Q2), relative standard deviation (RSD), model validity (Valid), reproducibility (Repr) and condition number (CN)

	R2	Q2	Valid	Repr	CN	RSD	Model
pyc	0.998	0.895	0.665	0.998	10.81	0.0009	original
	0.999	0.970	0.768	0.998	5.797	0.0006	adjusted
PSD	0.942	0.459	0.642	0.985	2.072	0.165	original
	0.947	0.796	0.765	0.968	2.327	0.071	adjusted
Fri	0.973	0.838	0.986	0.772	5.316	0.085	original
	0.616	0.272	0.786	0.819	3.432	0.253	adjusted
CE (no water)	0.962	0.724	0.756	0.975	4.20	2.45	original
	0.994	0.913	0.917	0.972	5.21	0.005	adjusted
LOD	0.964	0.904	0.878	0.941	2.072	0.704	original
	0.878	0.739	0.779	0.946	1.183	1.137	adjusted
sph	0.720	0.370	0.988	-0.2	4.20	0.015	original
	0.693	0.277	0.986	0.974	4.283	0.000	adjusted
app	0.520	0.321	0.816	0.760	1.183	0.028	adjusted
por	0.929	0.700	0.955	0.731	4.319	0.543	adjusted
avg	0.614	0.431	0.976	-0.200	1.316	0.005	adjusted
bulk	0.853	0.558	0.939	0.603	3.526	0.021	adjusted

The model for pycnometric density has low validity both with and without adjusted settings (Table 39). R2, Q2 and reproducibility values are good. Quadratic effects of plasticizer amount and the ratio between spray rate and powder feed rate had positive effect on

average pycnometric density. On the other hand the main effect of plasticizer was negative towards the density as were quadratic effects of temperature and batch size. The points fall nicely on line on observed-predicted graph.

Both particle size distribution models have low values of validity and predictability (Table 39). Reproducibility of the model is good. Observed and predicted values of PSD fall quite well to line and R2 is 0.95.

Adjusted model of friability has low R2, Q2, validity and reproducibility values (Table 39). Original model of friability has a bit lower reproducibility value, but other values are higher. RSD is quite big. From observed-predicted-graph can be seen that nothing really sits on the line and 10 (DOE9) is outlier (Appendix 5: Figure XIII). Other possible outliers are 2, 14 and 6 indicating that the model is not reliable.

For coating efficiency all the values are quite high (Table 39). R2 value is 0.99 and on the observed-predicted -graph the points fall on line quite well (Appendix 5: Figure XIII). Residuals have some curvature and DOE12 (8) is an outlier. This observed-predicted graph is for CE values that include water (graphs were calculated before the CE value without water was chosen as main CE value).

The original value model for the loss on drying has high or quite high values (Table 39). The adjusted version has lower values but they are still quite good.

Adjusted sphericity model has bad R2 and Q2 values but good validity and reproducibility (Table 39). Original sphericity has mediocre R2, bad Q2, good validity but negative reproducibility. Observed-predicted-graph shows scattered points.

Apparent density has low R2 and Q2 (Table 39). No real factor has been found for the model. Model isn't good and what can be told based on coefficients is that temperature had negative effect on density (Appendix 5). This is quite contradictory to the fact that

increased temperature should increase coalescence of the plasticized material. In Observed-predicted-graph DOE9 is also outlier, but other values don't seem to fall on the line either. Condition number is low (probably because temperature is the only variable of the model).

Porosity has good R2 and validity but Q2 and reproducibility values are 0.700 and 0.731 respectively (Table 39). The plasticizer amount gives a positive coefficient for porosity, this too is contradictory to the theory of plasticizing. It can be because plasticizer has increased the amount of coating and increased amount of coating has led to increase in porosity. Increases in rotor speed and in the ratio between spray rate and powder feed rate decrease the porosity. Rotor speed should increase coalescence and increased amount of sprayed water should increase adherence and plasticization of powder material.

R2 and Q2 values of average pore diameter model are low or mediocre, but validity is good (Table 39). Reproducibility is negative. Condition number is good (low amount of variables). It seems that plasticizer has some positive effect on the porosity (Appendix 5). This positive effect could be because increased amount of plasticizer increases the amount of coating. The only thing pointing to increasing effect of plasticizer is the quadratic effect of plasticizer in the adjusted model of CE and effect on PSD. From observed-predicted-graph it seems that the results of average pore diameter are quite scattered.

Bulk density model has low Q2 and low reproducibility and the model has large RSD (Table 39). Validity and R2 are good. Condition number is quite high. Quadratic factor of plasticizer amount has positive effect but main factor of plasticizer has negative effect (Appendix 5). Plasticizing increases the coalescence of coating polymers and thus density of the coating. Condition number is average (average amount of variables).

8.11 Optimization of the parameters

Modde 9.1 has optimization functionality which can be used as an aid to optimize the parameters of the coating equipment. The results wanted have to be determined and each

result is given a weight to emphasize how important that parameter or result is for the final product. Based on the models the software gives set of optimized parameters. These parameters can be used to produce a batch of pellets that should have wanted properties. Optimization was tried and some characterization was done of the resulting products (Table 40).

Table 40. Optimized settings and predictions made based on DOE results and the results from batches produced with settings. T = temperature, rot = rotor speed, plast = amount of plasticizer, PFR = powder feed rate, PSR = plasticizer spray rate, batch = batch size, Fri = friability, pyc = pycnometric density, LOD = loss on drying, CE = coating efficiency (with H_2O), P = predicted results, A = actual results

	T	rot	plast	PFR	PSR	batch	Span	Fri	pyc	LOD	CE (with H_2O)
P	71	470	30	8.5	0.64	500	0.42		0.0034	2.1	97
A							*0.0056*	*0.093*	*0.0029*	*5.8*	*100*
P	63	320	6.7	8	0.99	530	0.450	0.13	0.0014	2.2	96
A							*0.53*	*0.38*	*0.0007*	*2.4*	*93*
P	72	290	27	8	0.82	840	0.35	0.12	0.0014	3.3	100
A							*0.53*		*0.0014*	*2.8*	*86*
P	73	320	18	8	0.86	1000	0.45	0.13	0.0014	3.7	100
A							*0.44*			*2.9*	*94*

No weighting of parameters was used for the optimization in Table 41 and model for density (pyc) is not reliable, because it is unclear what it measures (only coating or coating and core beads). Actual results deviate from the predicted results quite a lot for all the produced batches. This can be because the combination of models that do not have optimum predictability. Another reason can be that characterization results are intervened and that characterization methods measure the wrong thing (or as in the case of CE (with H_2O) the results can be slightly misleading and should be treated). These calculations were

also conducted with CE values with water before CE without water were chosen as main CE value.

Both models for pycnometric density can be used but they have low validity and it is unclear what the method measures (Table 31) Both models for PSD have good values, but the original results (with DOE11 and DOE12) should not be used. Both friability models can be used, but the adjusted settings do not produce a good model. CE has good model at least with the adjusted settings. LOD produces good models. Apparent density model has R2 so low that it's barely significant and low Q2 value that makes the model bad (but significant). Porosity model can be used. Average pore diameter model should not be used because the reproducibility is negative. Bulk density model can be used but it has low predictability and low reproducibility. Sphericity values should not be used because the model has low predictability and original model has negative reproducibility.

If all the adjusted models (with DOE11.3 and DOE12.2) except average pore diameter are used for optimization, the weighing should be done so that the highest values go to pycnometric density, CE and LOD. Second highest values should go to PSD and porosity. Third highest values should go to bulk density and sphericity. Fourth highest values should go to friability and apparent density. Another option is to discard the worse models and only use those models that seem to be most reliable. When optimization settings are adjusted, target values should be given. If these target values are minimum or maximum values only upper limit or lower limit has to be set. If target value is something else than both lower and upper limits have to be specified. For example ±10 % values can be used as limits.

8.12 Stability of the method

Batches DOE10 and DOE14 were repeated with same parameters to determine the stability of the coating method. Variation of replicates' results is compared to the overall variation of the samples' results. This way a reproducibility value is produced for the models. High stability of the coating method is important for the applicability of the method. Great

variations in the replicate values would mean that the method is unreliable. Results of characterizations and their percentual differences and deviations are on Table 41.

Table 41. Variation of the center point replicates of the DOE.

	avg fri	LOD	Span	CE (no water)	sph	avg	bulk	app	por	avgpd
DOE10	0.15	5.50	0.66	94	0.84	1.45	1.18	1.52	22.0	0.06
DOE14	0.09	4.56	0.58	92	0.88	1.45	1.22	1.54	20.9	0.04
% diff	48.7	18.7	13.1	2.2	4.65	0.04	3.17	1.77	5.13	26.1
SD	0.04	0.67	0.06	1.4	0.03	0	0.03	0.02	0.78	0.01

Two replicates in the design is the minimum amount of replicates. In this case the small amount of replicates is a major disadvantage for the reliability of the method and the models. The reason for this is the fact that there are differences in the characterization results of the batches DOE10 and DOE14. Based on these two measurements the conclusion is that the coating method is not stable. There might be reason for the difference in unexplained variation of fluidizing flow during the DOE. DOE10 had too low fluidizing flow during coating phase and DOE14 had too high fluidizing flow during spheronization (and slightly too low flow during coating) (Appendix 4).

Fluidizing flow was set to 40 m^3/h during the whole coating process and it was kept constant during all the experiments. During the production of the DOE batches the volume per hour started to drift from the set value. During the experiment DOE6 the flow started to decrease. Decrease was more significant during the runs from DOE7 to DOE10. The drifting was thought to be the result of old and possibly partly clogged filters. After cleaning and changing the filters the problem was partly fixed. The flow did not decrease and for experiments DOE11 and DOE12 it was correct or almost correct. After these experiments the flow started to increase, especially during the spheronization. No explanation or permanent solution was found for this. The intensity of the vacuum of outlet

air was reduced by opening a gap (that could be adjusted) to the air removal system. The system was unstable.

Batches DOE7, DOE8, DOE9 and DOE10 were affected by too low fluidizing flow rate during the coating phase. If the velocity of the fluidizing flow is too low it is possible that the product bed is not fluidized (Dixit and Puthli 2009). This has an effect on all the coating properties. It is hard to guess the extent of the effect of the 10 - 15% drop in fluidizing flow but batches DOE7, DOE8 and DOE9 seem to have some irregularities in their results. Batches DOE13, DOE14 and DOE1 had too high fluidizing flow. Batches DOE11.3 and DOE12.2 were also affected by the drifting fluidizing flow but less than other affected batches. If the error in fluidizing flow had been constant, it would have been possible to use actual flow rate values in the model. Although this also would have caused problems with the definitive screening's fold-over mechanism.

8.13 Observed Equipment Limitations

Some of the results were sub-optimal because the equipment did not function as it was expected, when the parameters were chosen for the design of experiments. The screw feeder used for the powder feeding was not the suitable for some of the finer powders that were used in the experiments. The screw feeder also had some technical issues related to the operating of the equipment.. The rotation speed did not allow very slow velocities. The power switch of the equipment was unreliable. The rotation started at high speed for 0.5 - 1 seconds before adjusting to the set speed. Material takes a variable amount of time to travel from the funnel part to the pistol. To prevent this the powder should be turned on until the powder is at the end of the feeder and about to fall to the pistol part. At this point the feeding should be near constant until the end. Mass of the powder material can have some effect on the powder feed rate. Adhesiveness of the powder has effect on the powder feed rate. Some of the powder stays in the feeder even after the powder has stopped moving from feeder to pistol. The feeder should have some other agitator than the "vibrating" slope.

Agitator would guarantee more homogenous feeding and better feeding for difficult products.

The three-way-nozzle pistol has problems with gelation and clumping of powder in front of/at the tip of pistol. This can hinder the spraying by partially clogging the tip and by altering the shape or direction of the spray. Some of the powder is left in the pistol after spraying has stopped. The insertation of the pistol is done manually before the coating process begins and so is the removal of the pistol after coating and before spheronization. This part is operator dependent and could possibly affect the results.

The spray rate is dependent on the tube type and how tightly it is connected to the peristaltic pump. The spray rate is different for every liquid and it needs (or should be) measured for every mixture differently. This can be time consuming. A certain amount of liquid is in the tube all the time during spraying. The amount depends on the tube length and inner diameter and also the viscosity of spray liquid.

The scale of the rotor is inaccurate (50/100 rpm). The actual rotor speed cannot be seen on the machinery or in the program. During the process it would be good if product temperature could be followed. The actual gap width could also be good to see if adjustments need to be done during process. The amount of powder in the filters during the processing would be good to know (windows on upper part of equipment).

In GPCG 1 the filter bags can be shaken manually or automatically. During experiments the bags were shaken manually at random intervals. Shaking the bags and estimating the amount of loose powder is one way to visually observe how well the coating material adheres to core beads. There were some problems with the shaking of the filters during the process. The equipment has two-bag-filter system after expansion chamber and set of the bags would not shake regularly.

For this thesis the ambient temperature and humidity were left untouched but they should have been constant. These values were not measured.

9. CONCLUSIONS

The coating process was partly successful. The coating polymer adhered to substrate surface and formed a layer. The layer was not uniform and there were gaps in the layer. Erosion of the coating could be observed. The problems caused by drifting fluidizing flow and by some too extreme values in the DOE. These two problems and the uncertainties related to some of the characterization methods led to situation where complete optimization was not achieved.

Results of design of experiments were left inconclusive because optimization accomplished without all the critical quality attributes. With more knowledge about erosion rate and a more reliable coating efficiency method a better model for optimization could have been developed. Different weights on predictive models could have been tried.

The choice between non-working models and unrepresentative samples had to be made, but unfortunately there were no good choices. This could have been prevented with more thorough and systematic pre-testing before choosing the extremes for DOE. The lowest point for the rotor should have been 150 or 200 rpm. In an optimal situation (with a longer experimental period) the design should have been re-designed with higher low point for rotor speed and new batches should have been made. Also another DOE could have been executed after the first DOE. Also two replicate runs should have been made of every run to get better information on reproducibility and to minimize problems from outliers.

Most of the measurement equipment functioned reliably. QicPic and GRADIS feeder had problems with fine and adhesive materials (Carbomer). Pycnometer gave similar results

with and without drying the pellet samples. The paddle method for dissolution had problems with pellets that stuck to the paddle rods and to the bottom of the cups.

The swelling rate and the hydration rate of the pellet could have been examined with a single pellet. Pellets swelling rate could have been examined by weighting the pellet before hydration and at certain time points. The swelling rate could have been examined with an optical microscope and camera by taking pictures at certain time intervals.

The release rate or the erosion rate could have been examined with NMR method. The optimal plasticizing effect should have been examined beforehand from cast samples. Glass transition point could have been estimated beforehand with Gordon-Taylor or Fox equation. This way the spheronization (and coating) temperatures could have been adjusted to right levels according to amount of plasticizer in the formulation.

Fox equation for approximation of glass transition temperature is:

$$\frac{1}{Tg} = \sum_{i=1}^{n} \frac{Wi}{Tg,i}, \quad (5)$$

where w(Coating Polymer) is 70 - 99%,w(Plasticizer) is 1 - 30%, T_g(HPMC K4M) is approximately (Ford 1999; Watanabe and Ford 2004) 185 °C (458 K) and T_g(PEG400) is approximately - 60 °C (213 K) (Debeaufort and Voilley 1997).

T_g is 180°C with 1% of PEG400 and 67°C with 30% of PEG400 in formulation. The only batches of DOE that were spheronized above their estimated T_g values were DOE2 and DOE6. Amount of water should be taken to account. The glass transition temperature of water is 136 K (Capaccioli and Ngai 2011). In all the formulations there have been some amounts of water during the coating and spheronization phases. This can be seen from the LOD samples which were taken every 10 minutes during the whole coating process (Appendix 10).

The water content of the product is measured because it affects further processing, storage times, density etc. Water content of the final product should be as small as possible or at the same level as the starting materials. Extra water in the products is left in the coating, which is not the intention. The coating formulation is only supposed to have polymer and plasticizer.

The run order was randomized, but replicates should have been made and the operator should have been unaware of the formulation of the batches. All QicPic batches should have been run with the same settings (maximum settings so that even the troublesome batches could have passed the gaps in the equipment). Selection of pellets for the SEM pictures was done so that pellets were picked with tweezers and the sample maker had to choose certain pellets from batches. A method that selects random pellets from the entire batch should have been developed. Imaging was also done only for one pellet of the selected pellets. All pellets on the tabs should have been imaged and evaluated. Only a small amount of pellets were chosen for pycnometric density measurement. This could have been affected by sampling bias and segregation. A sampling method that takes pellets from the entire batch randomly should have been developed. Weighting of the samples for the dissolution took only the most adhesive material (that stuck to the sampling equipment). A random sampling method should have been developed.

The coating method was partly successful. Coating material adhered to the pellet surface and the process could be partly adjusted. Some relationships between the formulation, the coating settings and the properties of the coating could be seen. With some of the suggestions mentioned earlier it should be possible to develop a coating method that meets the objectives of this thesis.

ACKNOWLEDGEMENTS

I want to thank Katrin Walter, Susanna Abrahmsén Alami, Anne Juppo and everybody else who helped me with my thesis.

10. REFERENCES

Alderman DA: A review of cellulose ethers in hydrophilic matrices for oral controlled release dosage forms. Int J Pharm, Tech. & Prod. Mfr., 5: 1-9, 1984

Antony J: Design of Experiments for Engineers and Scientists. 1st edition. Butterworth-Heinemann, UK, Oxford, 2003

Atarés L, Depypere F, Pieters JG and Dewettinck K: Coating quality as affected by core particle segregation in fluidized bed processing. J Food Eng 113: 415–421, 2012

Aulton ME and Taylor KMG: Aulton's Pharmaceutics: The Design and Manufacture of Medicines: Modified-release peroral dosage forms, 483 - 499. Churchill Livingstone/Elsevier, 2007

Bellehumeur CT, Kontopoulou M, Vlachopoulos J: The role of viscoelasticity in polymer sintering. Rheol Acta 37: 270–278, 1998

Bilancetti L, Poncelet D, Catherine Loisel, Stefania Mazzitelli, and Claudio Nastruzz: A Statistical Approach to Optimize the Spray Drying of Starch Particles: Application to Dry Powder Coating. AAPS PharmSciTech, Vol. 11, No. 3, 2010

Bodmeier R and Paeratakul O: Process and Formulation variables affecting the drug release from chlorpheniramine maleate-loaded beads coated with commercial and self-prepared aqueous ethyl cellulose pseudolatexes. Int J Pharm 70: 59-68, 1991

Bodmeier R and Paeratakul O: The effect of curing on drug release and morphological properties of ethylcellulose pseudolatex-coated beads. Drug Dev Ind Pharm 20 (9): 1517 – 1533, 1994

Bodmeier R: Tableting of coated pellets. Eur J Pharm Biopharm 43: l-8, 1997

Bouffard J, Dumont H, Bertrand F and Legros R: Optimization and scale-up of a fluid bed tangential spray rotogranulation process. Int J Pharm 335: 54 – 62, 2007

Capaccioli S and Ngai KL: Resolving the controversy on the glass transition temperature of water? J Chem Phys 135, 104504, 2011

Cerea M, Zheng W, Young CR, McGinity JW: A novel powder coating process for attaining taste masking and moisture protective films applied to tablets. Int J Pharm 279: 127–139, 2004

Cole GC: Introduction and overview of pharmaceutical coating. Book: Pharmaceutical Coating Technology, p. 1-5. Edited by Cole G. Taylor & Francis Ltd. 1995

Cole GC: The coating process. Book: Pharmaceutical Coating Technology, p. 170-203. Edited by Cole G. Taylor & Francis Ltd. 1995

Colombo P, Bettini R, Santi P and Peppas NA: Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. PSTT Vol. 3, No. 6, 2000

Debeaufort F and Voilley A: Methylcellulose-Based Edible Films and Coatings: 2. Mechanical and Thermal Properties as a Function of Plasticizer Content. J Agric Food Chem 45, 685-689, 1997

Dixit R and Puthli S: Fluidization Technologies: Aerodynamic Principles and Process Engineering. J Pharm Sci, VOL. 98, 11, 2009

Felton LA and McGinity JW: Influence of Insoluble Excipients on Film Coating Systems. Drug Dev Ind Pharm, 28(3): 225–243, 2002

Ford JL: Thermal analysis of hydroxypropylmethylcellulose and methylcellulose: powders, gels and matrix tablets. Int J Pharm 179, 209–228, 1999

Fukumori Y and Ichikawa H: Fluid Bed Processes for Forming Functional Particles. Encyclopedia of Pharmaceutical Technology, Volumes 1- 6, 3rd edition. Edited by Swarbrick J. 2006

Gajdziok J, Bernatoniene J, Muselík J, Masteiková R, Dvořáčková K, Petkeviciute Z, Lazauskas R, Kalveniene Z, and Bernatoniene R: The evaluation of formulations for the preparation of new formula pellets. Pharm Dev Technol, 16(5): 520–528, 2011

Gao P and Meury RH: Swelling of Hydroxypropyl Methylcellulose Matrix Tablets. 1. Characterization of Swelling Using a Novel Optical Imaging Method. J Pharm Sci 85, 7: 725 – 731, 1996

Gazzaniga A, Palugan L, Foppoli A, Sangalli ME: Oral pulsatile delivery systems based on swellable hydrophilic polymers. Eur J Pharm Biopharm 68: 11–18, 2008

Gazzaniga A, Iamartino P, Maffione G, Sangalli ME: Oral delayed-release system for colonic specific delivery. Int J Pharm 108: 77-83, 1994

Ghebre-Sellassie I: Pellets: A General Overview. Pharmaceutical Pelletization Technology. p. 1-13, 1st edition, Drugs and the Pharmaceutical Sciences vol. 37. Edit. Ghebre-Sellassie I, Marcel Dekker, Inc. New York 1989

Golbraikh A, Tropsha A: Beware of q2! J Mol Graph Model 20: 269–276, 2002

Guignon B, Regalado E, Duquenoy A, Dumoulin E: Helping to choose operating parameters for a coating fluid bed process. Powder Technol 130: 193– 198, 2003

Hata T, Kodani M, Ueda S, Ueda Y, Yamaguchi H: Time-controlled explosion systems and processes for preparing the same. US Patent 4871549 A, 1989

Heng PWS, Chan LW, Chew SH: Mechanism of Pellet Coat Rupture and Its Effect on Drug Release. Chem Pharm Bull 47 (7): 939-943, 1999

Hogan JE: Film-coating materials and their properties. Book: Pharmaceutical Coating Technology, p. 6-50. Edited by Cole G. Taylor & Francis Ltd. 1995

ISO 11357-2:2013: Plastics -- Differential scanning calorimetry (DSC) -- Part 2: Determination of glass transition temperature and glass transition step height

Jones DM and Percel PJ: Coating of Multiparticulates Using Molten Materials: Formulation and Process Considerations. Multiparticulate Oral Drug Delivery. p 113-142, 1st edition, Drugs and the Pharmaceutical Sciences vol. 65. Edit. Ghebre-Sellassie I, Marcel Dekker, Inc. New York 1994

Kablitz CD and Urbanetz NA: Characterization of the film formation of the dry coating process. Eur J Pharm Biopharm 67: 449–457, 2007

Kablitz CD 2007 Dry coating - a characterization and optimization of an innovative coating technology. PhD.

Kablitz CD, Kappl M, Urbanetz NA: Parameters influencing polymer particle layering of the dry coating process. Eur J Pharm Biopharm 69: 760–768, 2008

Kablitz CD, and Nora Anne Urbanetz: Stability of dry coated solid dosage forms. Pharm DevTech 14 (6): 613–622, 2009

Kablitz CD and Urbanetz NA: Evaluating the process parameters of the dry coating process using a 25-1 factorial design. Pharm Dev Tech, 18 (1): 39–45, 2003

Kao CC, Chen SC, Sheu MT: Lag time method to delay drug release to various sites in the gastrointestinal tract. J Control Release 44: 263 - 270, 1997

Kavanagh N and Corrigan OI: Swelling and erosion properties of hydroxypropylmethylcellulose (Hypromellose) matrices—influence of agitation rate and dissolution medium composition. Int J Pharm 279: 141 – 152, 2004

Knoch A and Ghebre-Sellassie I: Pelletization technique, Enc Pharm Tech, 2002

Li CL, Martini LG, Ford JL and Roberts M: The use of hypromellose in oral drug delivery. JPP 57: 533–546, 2005

Malaterre V, Ogorka J, Loggia N, Gurny R: Approach to design push–pull osmotic pumps. Int J Pharm 376: 56 - 62, 2009

Maruyama N, Kokubo H , Nishiyama Y: Method of manufacturing a solid preparation coated with non-solvent coating. Patent US 5789014 A. Published 4.8.1998

Mastropietro DJ and Omidian H: Prevalence and trends of cellulosics in pharmaceutical dosage forms. Drug Dev Ind Pharm, 39: 382–392, 2013

Medscape: http://emedicine.medscape.com/article/1174981-overview Rutchik JS, Seidman RJ, Talavera F, Lopate G, Benbadis SR and Ramachandran TS: Organic Solvents. Medscape: Updated 4.4.2012

Mettler Toledo: Operating instructions HR73 and HG53 Moisture Analyzers HR73-P and HG53-P Moisture Analyzers. Mettler-Toledo GmbH, Laboratory & Weighing Technologies, CH-8606 Greifensee, Switzerland, 2001

Micromeritics: Porosimetry Brochure. 2001

Muramatsu M, Kanada K, Nishida A, Ouchi K, Saito N, Yoshida M, Shimoaka A, Ozeki T, Yuasa H and Kanaya Y: Application of Carbopol® to controlled release preparations I. Carbopol® as a novel coating material. Int J Pharm 199: 77–83, 2000

Olsen KW: Fluid Bed Equipment. Pharmaceutical Pelletization Technology. p. 39-70, 1st edition, Drugs and the Pharmaceutical Sciences vol. 37. Edit. Ghebre-Sellassie I, Marcel Dekker, Inc. New York 1989

Omidian H, Rocca JG, Park K: Advances in superporous hydrogels. J Control Release 102: 3 –12, 2005

OSHA (Occupational Safety & Health Administration): https://www.osha.gov/ visited 07.01.2014

Patent: EP 1711169 A1: Extended release coated microtablets of venlafaxine hydrochloride. 2006

Parikh DM, Bonck JA and Mogavero M: 9. Batch Fluid Bed Granulation. Handbook of Pharmaceutical Granulation Technology. Drugs and the Pharmaceutical Sciences vol. 81. Edited by Parikh DM. Marcel Dekker, inc. 1st edition. New York. 1997

Peacock AJ and Calhoun A: 1. Introduction to Synthetic Polymers. Polymer Chemistry - Properties and Application. Edited by Peacock AJ and Calhoun A. Hanser Publishers. 2006

Pearnchob N and Bodmeier R: Dry polymer powder coating and comparison with conventional liquid-based coatings for Eudragit RS, ethylcellulose and shellac. Eur J Pharm Biopharm 56: 363–369, 2003

Pearnchob N and Bodmeier R: Coating of pellets with micronized ethylcellulose particles by a dry powder coating technique. Int J Pharm 268: 1–11, 2003

Pearnchob N and Bodmeier R: Dry Powder Coating of Pellets with Micronized Eudragit® RS for Extended Drug Release. Pharmaceutical Research, 20, (12): 1970 – 1976, 2003

Peppas NA, Bures P, Leobandung W and Ichikawa H: Hydrogels in pharmaceutical formulations. Eur J Pharm Biopharm 50: 27 – 46, 2000

Pisek R, Planinsek O, Tus M and Srcic S: Influence of Rotational Speed and Surface of Rotating Disc on Pellets Produced by Direct Rotor Pelletization. Pharm Ind 62, 4: 312 – 319, 2000

Politis SN and Rekkas DM: Pelletization Processes for Pharmaceutical Applications: A Patent Review. Recent Pat Drug Delivery & Formulation 5: 61-78, 2011

PubChem: http://pubchem.ncbi.nlm.nih.gov/ (Search term “polymer” 24.10.2013)

Salsa T, Veiga F and Pina ME: Oral Controlled-Release Dosage Forms. I. Cellulose Ether Polymers in Hydrophilic Matrices. Drug Dev Ind Pharm, 23, 929-938, 1997

Sauer D, Zheng W, Coots LB and McGinity JW: Influence of processing parameters and formulation factors on the drug release from tablets powder-coated with Eudragit L 100-55. European J Pharm Biopharm 67: 464–475, 2007

Sauer D and McGinity JW: Influence of additives on melt viscosity, surface tension, and film formation of dry powder coatings. Drug Dev Ind Pharm 35(6): 646–654, 2009

Sauer D, Cerea M, DiNunzio J, McGinity J: Dry powder coating of pharmaceuticals: A review. Int J Pharm 2013

Shin-Etsu: http://www.metolose.jp/e/pharmaceutical/aqoat.shtml visited 6.10.2013

Smikalla M, Axel Mescherb, Peter Walzelb, Nora Anne Urbanetz: Impact of excipients on coating efficiency in dry powder coating. Int J Pharm 405: 122–131, 2011

Sperling LH: Introduction to Polymer Science. Introduction to Physical Polymer Science. John Wiley & Sons, New Jersey, 2006

Strobl G: 1 Constitution and Architecture of Chains. The Physics of Polymers: Concepts for Understanding Their Structures and Behavior. 3rd edition. Springer-Verlag Berlin Heidelberg, 2007

Tahara K, Yamamoto K, Nishihata T: Overall mechanism behind matrix sustained release (SR) tablets prepared with hydroxypropyl methylcellulose 2910. J Control Release 35: 59-66, 1995

Terebesi I and Bodmeier R: Optimised process and formulation conditions for extended release dry polymer powder-coated pellets. European J Pharm Biopharm 75: 63–70, 2010

The Montreal Protocol, 2009 (http://ozone.unep.org/new_site/en/index.php) visited 6.10.2013

Vertommen and Kinget: The Influence of Five Selected Processing and Formulation Variables on the Particle Size, Particle Size Distribution, and Friability of Pellets Produced in a Rotary Processor. Drug Dev Ind Pharm, 23: 39-46, 1997

Watanabe T and Ford JL: Influence of sample pan design on the thermal characterisation of some cellulose derivatives. School of Pharmacy & Chemistry, Liverpool John Moores University, JPP, 56, 2004

Williams PA: 1. Introduction. Handbook of Industrial Water Soluble Polymers. John Wiley & Sons edited by Williams PA, 2007

Williams PA: 4. Gelling Agents. Handbook of Industrial Water Soluble Polymers. John Wiley & Sons edited by Williams PA, 2007

Wolfram Math World: http://mathworld.wolfram.com/CorrelationCoefficient.html visited 09.04.2014

Yamamoto S, Taniguchi H, Hayashi H, Hori K, Tsujimura T, Nakamura Y, Sato H and Inoue M: How do tablet properties influence swallowing behaviours? J Pharm Pharmacol, In press, 2013

Zhang X, Tang X and Yang R: Development of a Tamsulosin Hydrochloride Controlled-Release Capsule Consisting of Two Different Coated Pellets. Drug Dev Ind Pharm, 35: 26–33, 2009

APPENDICES

Appendix 1.

Table I. Formulation of batches produced during pre-tests.

Batch	**coating polymer**	**plasticizer**	**cores**	**wetting**	**binder**
11092013	HPMC K100	0	cellets	H_20	6% HPMC 3cP
12092013	HPMC K100	0	cellets	H_20	6% HPMC 3cP
16092013	HPMC K100	0	CP507	H_20	6% HPMC 3cP
18092013	HPMC K100	0	CP507	H_20	H20
19092013	HPMC K100	0	CP507	H_20	6% HPMC 3cP
23092013	HPMC K4M	0	CP507	H_20	6% HPMC 3cP
25092013	HPMC K4M	PEG400	CP507	H_20	3% HPMC 3cP
26092013.1	HPMC K4M	PEG400	CP507	H_20	3% HPMC 3cP
26092013.2	HPMC K100	0	CP507	H_20	6% HPMC 3cP
27092013	HPMC K100	0	CP507	H_20	6% HPMC 3cP
30092013	HPMC K100	0	CP507	H_20	6% HPMC 3cP
01102013	HPMC K100	0	CP507	6% HPMC 3cP	6% HPMC 3cP
02102013	HPMC K100	PEG400	CP507	PEG400	0
03102013	HPMC K100	PEG400	CP507	PEG400	0
09102013.1	Carpobol (granule)	PEG400	CP507	PEG400	0
09102013.1	Carbopol (granule)	0	CP507	water	0
14102013	Carbopol (fine)	0	CP507	ethanol	3% HPC JF
15102013	HPMC K4M	PEG400	CP507	PEG400	0
16102013	HPMC K4m	ATEC	CP507	ATEC	0

Table II. Process parameters of batches produced during pre-tests.

Batch	rotor speed	spheronization temp (C)	spheronization time (min	wetting time (min)	drying temp (C)	drying time (min)
11092013	150/200	0	0	5	40	10
12092013	150/300	0	0	5	80	25
16092013	300	30	20	5	50	10
18092013	300	30	20	5	50	10
19092013	300	30	20	5	50	10
23092013	300	30	10	5	60	10
25092013	300	30	20	5	60	10
26092013.1	300	30	60	5	60	10
26092013.2	150	30	20	5	50	10
27092013	150	30	60	5	50	10
30092013	150	60	20	5	60	10
01102013	150	60	20	5	0	0
02102013	150	60	20	5	0	0
03102013	150	60	20	1	0	0
09102013.1	150	0	0	1	0	0
09102013.2	150	0	0	1	0	0
14102013	150	0	0	1	0	0
15102013	150	60	20	1	0	0
16102013	150	60	20	1	0	0

Appendix 2.

Table III. Results for DOE batches produced with original settings (average friability = avgf; loss on drying = LOD; coating efficiency = CE; sphericity of x50 = sph50; average pycnometric density = pyc)

	avgf	LOD	Span	CE	sph50	pyc
DOE1	0.16	9.40	0.50	79.4	0.85	1.45
DOE2	0.55	4.74	0.43	91.8	0.88	1.45
DOE3	0.24	6.09	0.45	89.7	0.88	1.45
DOE4	0.08	2.60	0.78	86.0	0.87	1.46
DOE5	0.53	6.70	0.65	90.7	0.82	1.47
DOE6	0.89	2.12	0.61	90.8	0.82	1.44
DOE7	0.40	3.94	0.50	87.2	0.88	1.47
DOE8	0.42	9.52	0.41	98.3	0.89	1.44
DOE9	0.10	10.00	0.68	117	0.84	1.44
DOE10	0.15	5.50	0.66	93.9	0.84	1.45
DOE11	0.46	6.25	1.31	99.4	0.86	1.46
DOE12	0.24	9.40	2.14	94.2	0.84	1.44
DOE13	0.28	2.84	0.53	88.4	0.85	1.45
DOE14	0.09	4.56	0.58	92.0	0.88	1.45
mean	0.33	5.98	0.73	92.8	0.86	1.45
SD	0.23	2.73	0.46	8.59	0.02	0.01
median	0.26	5.80	0.59	91.3	0.86	1.45
min	0.08	2.12	0.41	79.4	0.82	1.44
max	0.89	10.00	2.14	117	0.89	1.47

Table IV. Results for DOE batches produced with adjusted settings (average friability = avgf; loss on drying = LOD; coating efficiency = CE; sphericity of x50 = sph50; average pycnometric density = pyc; bulk density = bulk; apparent density = app; porosity = por; average pore diameter = avgpd)

	avgf	LOD	Span	CE	sph50	pyc	bulk	app	por	avgpd
DOE1	0.16	9.40	0.50	79.4	0.85	1.45	1.23	1.54	20.3	0.05
DOE2	0.55	4.74	0.43	91.8	0.88	1.45	1.24	1.53	18.7	0.05
DOE3	0.24	6.09	0.45	89.7	0.88	1.45	1.24	1.57	20.9	0.04
DOE4	0.08	2.60	0.78	86.0	0.87	1.46	1.21	1.53	20.8	0.04
DOE5	0.53	6.70	0.65	90.7	0.82	1.47	1.25	1.56	19.5	0.04
DOE6	0.89	2.12	0.61	90.8	0.82	1.44	1.18	1.51	21.9	0.05
DOE7	0.40	3.94	0.50	87.2	0.88	1.47	1.27	1.55	18.0	0.03
DOE8	0.42	9.52	0.41	98.3	0.89	1.44	1.27	1.59	20.0	0.06
DOE9	0.10	10.00	0.68	117	0.84	1.44	1.35	1.66	18.6	0.04
DOE10	0.15	5.50	0.66	93.9	0.84	1.45	1.18	1.52	22.0	0.06
DOE11.3	0.54	4.88	1.79	90.2	0.86	1.46	1.27	1.54	17.9	0.04
DOE12.2	0.98	10.39	2.44	83.6	0.86	1.44	1.24	1.56	20.6	0.06
DOE13	0.28	2.84	0.53	88.4	0.85	1.45	1.24	1.50	17.4	0.04
DOE14	0.09	4.56	0.58	92.0	0.88	1.45	1.22	1.54	20.9	0.04
mean	0.39	5.95	0.79	91.4	0.86	1.45	1.24	1.55	19.8	0.05
SD	0.29	2.85	0.59	8.66	0.02	0.01	0.04	0.04	1.50	0.01
median	0.34	5.19	0.59	90.4	0.86	1.45	1.24	1.54	20.1	0.04
min	0.08	2.12	0.41	79.4	0.82	1.44	1.18	1.50	17.4	0.03
max	0.98	10.39	2.44	117	0.89	1.47	1.35	1.66	22.0	0.06

Appendix 3.

Table V. Pearson's correlations and coefficients of determination for DOE responses

Response 1	Response2	Correlation *r*	r^2
avg fria	LOD	0.046	0.002
avg fria	span	0.558	0.311
avg fria	CE	-0.234	0.055
avg fria	sph	-0.230	0.053
avg fria	avg pyc den	-0.195	0.038
avg fria	bulk den	-0.152	0.023
avg fria	app den	-0.179	0.032
avg fria	por	0.035	0.001
avg fria	avg pore d	0.273	0.074
LOD	span	0.284	0.081
LOD	CE	0.222	0.049
LOD	sph	0.038	0.001
LOD	avg pyc den	-0.389	0.152
LOD	bulk den	0.501	0.251
LOD	app den	0.700	0.490
LOD	por	0.029	0.001
LOD	avg pore d	0.409	0.167
span	CE	-0.183	0.033
span	sph	-0.072	0.005
span	avg pyc den	-0.006	0.000
span	bulk den	0.047	0.002
span	app den	0.045	0.002
span	por	-0.025	0.001
span	avg pore d	-0.006	0.000
CE	sph	-0.104	0.011

CE	avg pyc den	-0.297	0.088
CE	bulk den	0.635	0.403
CE	app den	0.701	0.492
CE	por	-0.209	0.044
CE	avg pore d	-0.173	0.030
sph	avg pyc den	0.051	0.003
sph	bulk den	0.162	0.026
sph	app den	0.111	0.012
sph	por	-0.159	0.025
sph	avg pore d	0.051	0.003
avg pyc den	bulk den	0.021	0.000
avg pyc den	app den	-0.198	0.039
avg pyc den	por	-0.314	0.099
avg pyc den	avg pore d	-0.606	0.367
bulk den	app den	0.852	0.725
bulk den	por	-0.689	0.474
bulk den	avg pore d	-0.464	0.215
app den	por	-0.207	0.043
app den	avg pore d	-0.135	0.018
por	avg pore d	0.676	0.458

Table VI. Example of correlation matrix with definitive screening

	Temp	Rot	Pla	Pow	Po2	Bat	Temp*Temp	Rot*Rot	Pla*Pla	Bat*Bat	Temp*Pla	den	Par	Fri~	LOD~	ce~
Temp	1	0	0	0	0	0	0	0	0	0	0	0,179025	-0,12547	0,164949	-0,74278	-0,72421
Rot	0	1	0	0	0	0	0	0	0	0	0	0,039452	-0,49364	-0,20515	-0,20175	-0,05637
Pla	0	0	1	0	0	0	0	0	0	0	0	-0,64879	-0,29013	0,265971	0,077672	0,03122
Pow	0	0	0	1	0	0	0	0	0	0	0	-0,17299	0,34719	-0,57126	0,355003	0,359443
Po2	0	0	0	0	1	0	0	0	0	0	0	0,240644	-0,35421	-0,36319	-0,19878	-0,17147
Bat	0	0	0	0	0	1	0	0	0	0	0	-0,21929	-0,19794	-0,07537	0,445598	0,471363
Temp*Temp																
Rot*Rot	0	0	0	0	0	0	1	0,3	0,3	0,3	0	-0,1607	0,244113	0,35001	0,033154	0,041006
Pla*Pla	0	0	0	0	0	0	0,3	1	0,3	0,3	0,41833	0,041071	0,174141	0,492794	0,103744	0,098273
Bat*Bat	0	0	0	0	0	0	0,3	0,3	1	0,3	0	0,22204	-0,34993	0,351412	0,09731	0,075876
Temp*Pla	0	0	0	0	0	0	0,3	0,3	0,3	1	-0,41833	-0,16222	0,212532	0,016704	0,151496	0,08448
den	0	0	0	0	0	0	0	0,41833	0	-0,41833	1	-0,18454	-0,1217	0,263065	-0,0305	0,189926
Par	0,179025	0,039452	-0,64879	-0,17299	0,240644	-0,21929	-0,1607	0,041071	0,22204	-0,16222	-0,18454	1	-0,0923	-0,01211	-0,38261	-0,48787
Fri~	-0,12547	-0,49364	-0,29013	0,34719	-0,35421	-0,19794	0,244113	0,174141	-0,34993	0,212532	-0,1217	-0,0923	1	-0,04326	0,28983	0,173996
LOD~	0,164949	-0,20515	0,265971	-0,57126	-0,36319	-0,07537	0,35001	0,492794	0,351412	0,016704	0,263065	-0,01211	-0,04326	1	-0,17341	-0,23761
ce~	-0,74278	-0,20175	0,077672	0,355003	-0,19878	0,445598	0,033154	0,103744	0,09731	0,151496	-0,0305	-0,38261	0,28983	-0,17341	1	0,941559
	-0,72421	-0,05637	0,03122	0,359443	-0,17147	0,471363	0,041006	0,098273	0,075876	0,08448	0,189926	-0,48787	0,173996	-0,23761	0,941559	1

Table VII. Error of method based on the replicate runs DOE10 and DOE14

	Fri %	LOD %	Span	CE %	Sph x50	Pyc Den	Bulk Den	App Den	Por	Avg Por D (um)
DOE10	0.2	5.5	0.7	94.0	0.8	1.4	1.2	1.5	22.0	0.1
DOE14	0.1	4.6	0.6	92.0	0.9	1.4	1.2	1.5	20.9	0.0
%difference	48.7	18.7	13.1	2.2	4.7	0.0	3.2	1.8	5.1	26.1
SD	0.0	0.7	0.1	1.4	0.0	0.0	0.0	0.0	0.8	0.0

Appendix 4.

Table VIII. Drifting of fluid flow during DOE runs

t (m)	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D13	D14	D1	D12.2	D11.3
0	40.3															
1		40.1	40.0	39.9	39.4	38.9	37.9	35.1	35.6		40.3		40.2		42.0	
2										40.1		40.0		40.8		41.9
3								35.3								
4	40.1	40.1			39.0	38.4	37.6						40.1			
5			39.9	40.2								40.0			40.9	
6	40.0								35.4		40.0					41.7
7								35.2								
8				40.1	39.1	38.2				40.0						
9			40.0								40.0				39.9	
11													40.0			40.4
12		39.9			38.9		37.2	34.8	34.7					41.2	39.8	
13	39.9											40.0				
14										40.0						
15		40.1				37.4					40.8					
16	40.1														41.0	
17			39.9													40.8
18	40.1															
19		40.0		40.0	38.4	36.8			34.1				38.1			
21												40.0			39.6	
22	40.5						36.4	34.0						40.9		41.0
23			40.0							40.0	40.0					
24																
25		40.0							33.7							40.4
26					38.1											
27				40.0		40.1		33.5					38.3			
28		41.2	40.0											41.0		
29					40.4		35.7	33.5			40.0				39.4	40.4
30	39.9															
31				40.0		39.9				40.0						
32					39.9										40.3	
33												40.0	48.0			
34					39.9						40.0					
35			40.0											41.0		
37								40.0	40.0	40.3						40.1
38	40.0	40.0	40.0			40.0										
39					40.0											
40																
41				40.0										41.3		
42									40.0	38.5		39.9	46.4			
43																39.9
44							40.3									
45																
46					40.1					38.3						
47								40.0	40.1					50.4		
48				40.1												
51										38.3						
52							40.0									40.5
54										38.2				50.0		
58												40.0				
61				40.1										46.8		
69												40.0				
70				40.0												
78												44.4				
92												42.5				

Appendix 5.

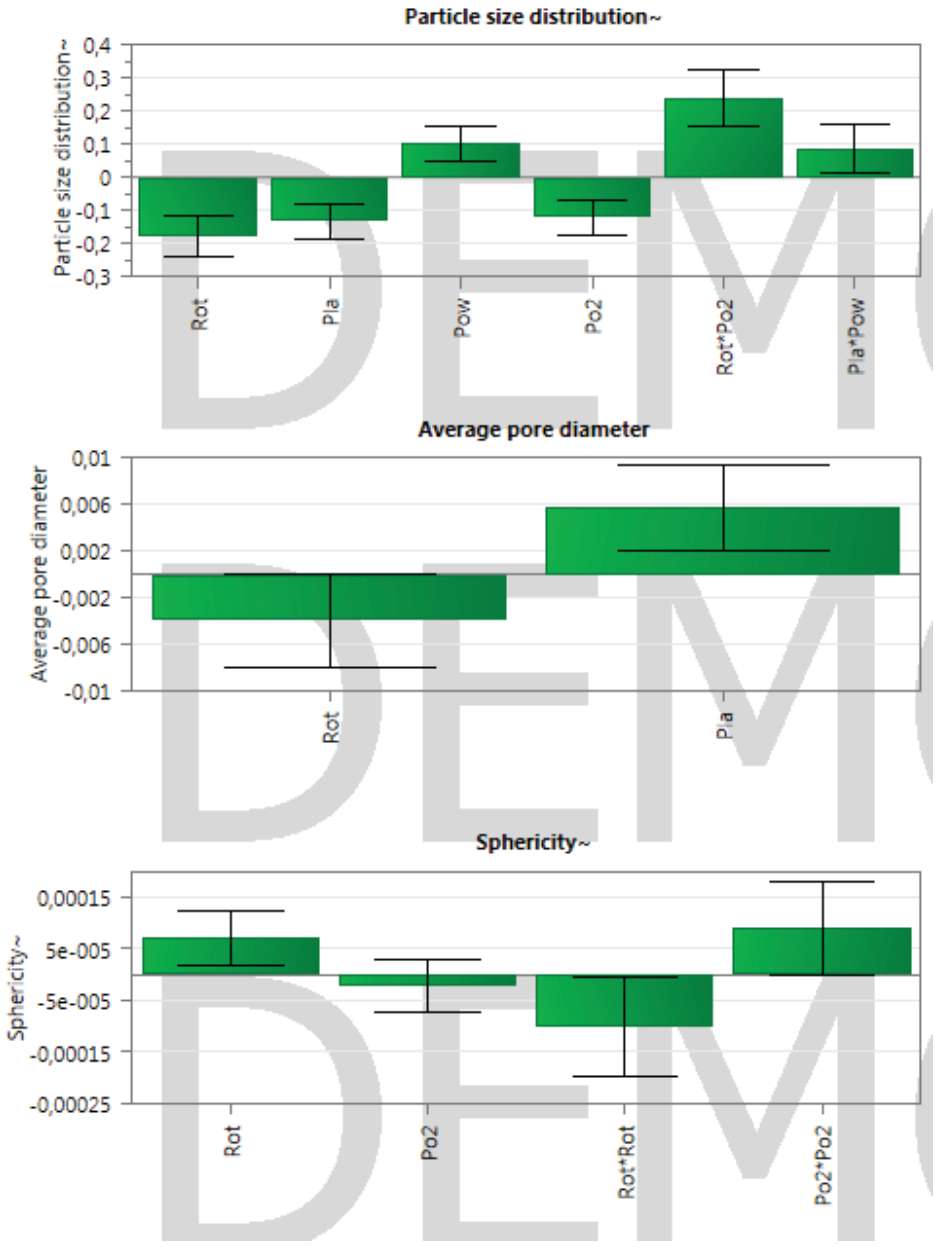


Figure IX. Coefficients of models with adjusted settings

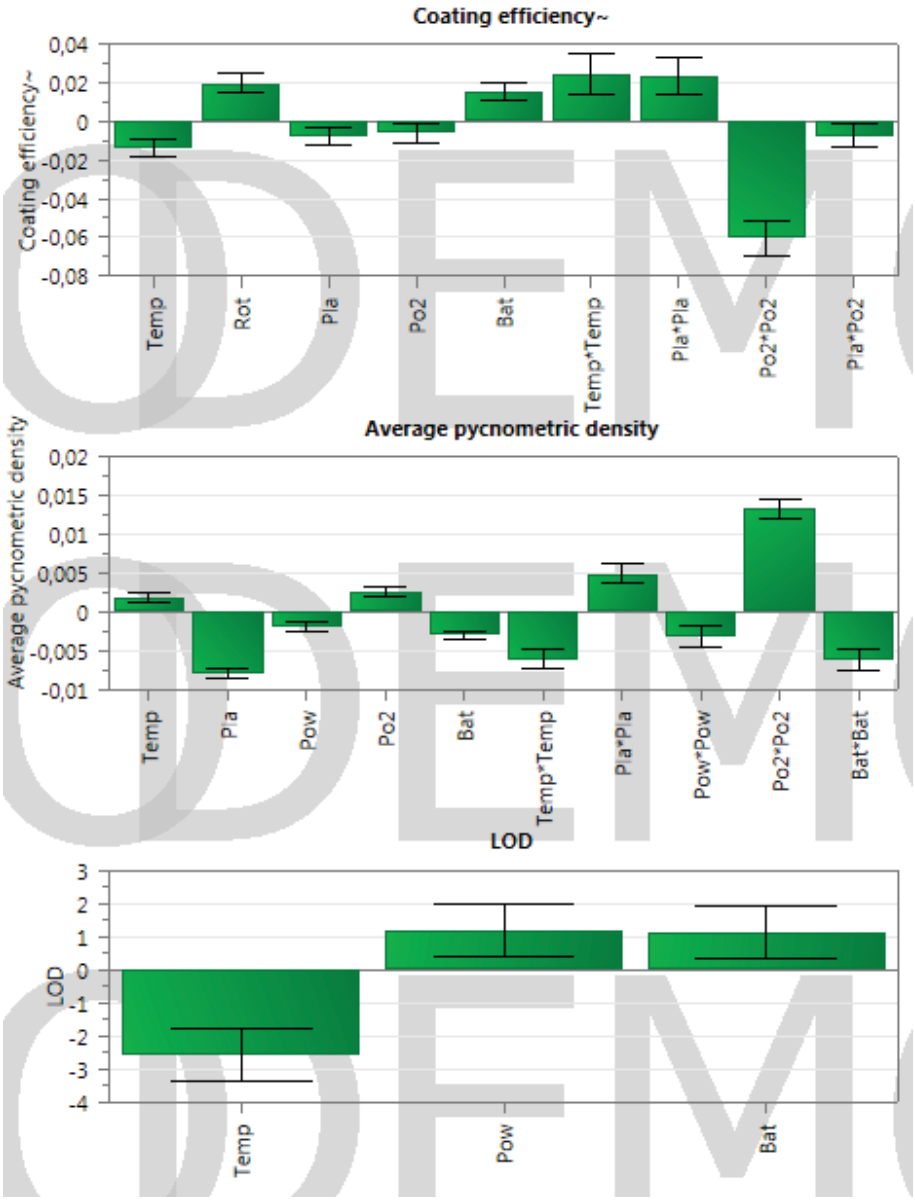


Figure X. Coefficients of models with adjusted settings

Figure XI. Coefficients for models with adjusted settings

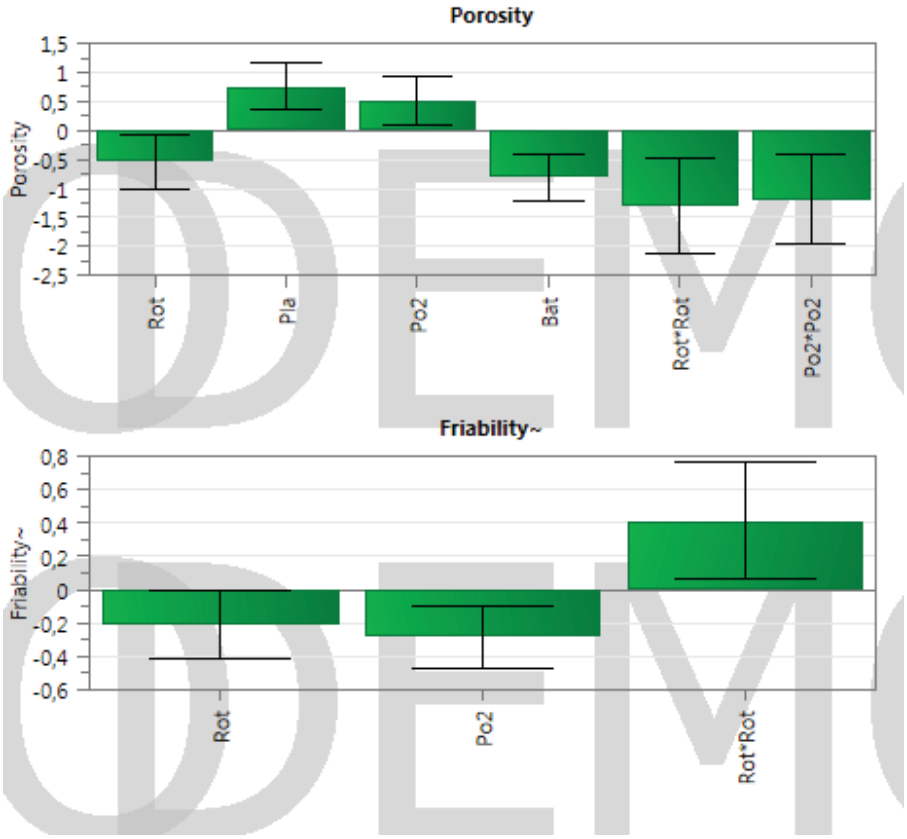
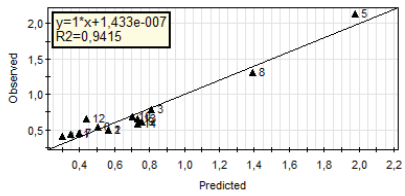
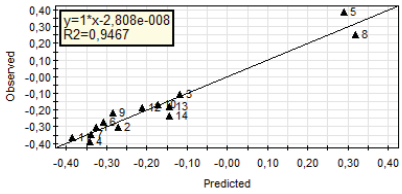


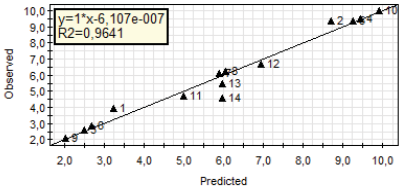
Figure XII. Coefficients for models with adjusted settings



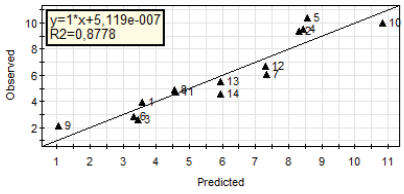
PSD orig.



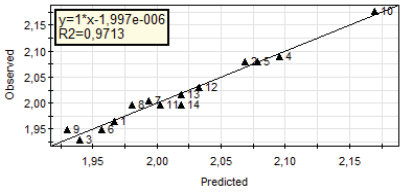
PSD adj.



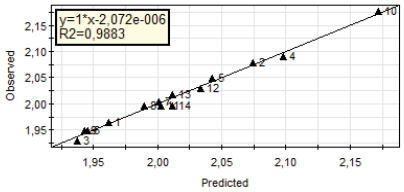
LOD orig



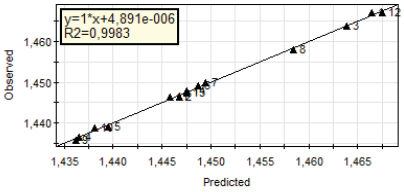
LOD adj.



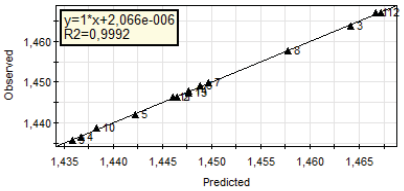
CE orig.



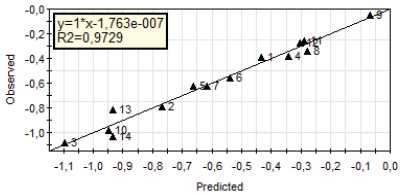
CE adj.



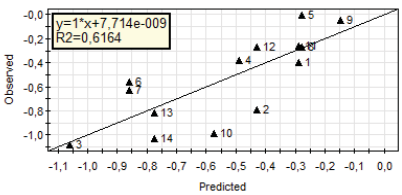
Pyc den orig.



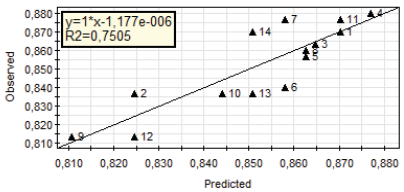
Pyc den adj.



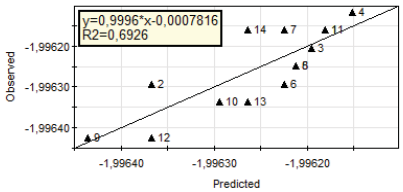
Fri orig.



Fri adj.



Sph orig.



Sph adj.

Figure XIII. Observed - Predicted points for models (CE with H_2O) with original settings (DOE11 and DOE12) and with adjusted settings

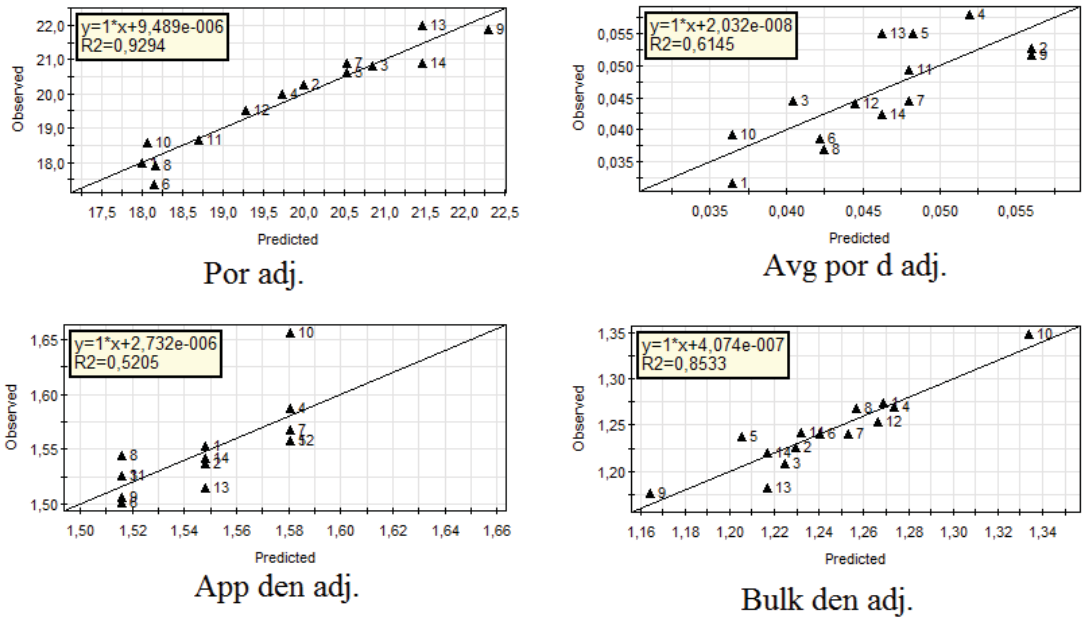


Figure XIV. Observed - Predicted points for models

Appendix 6.

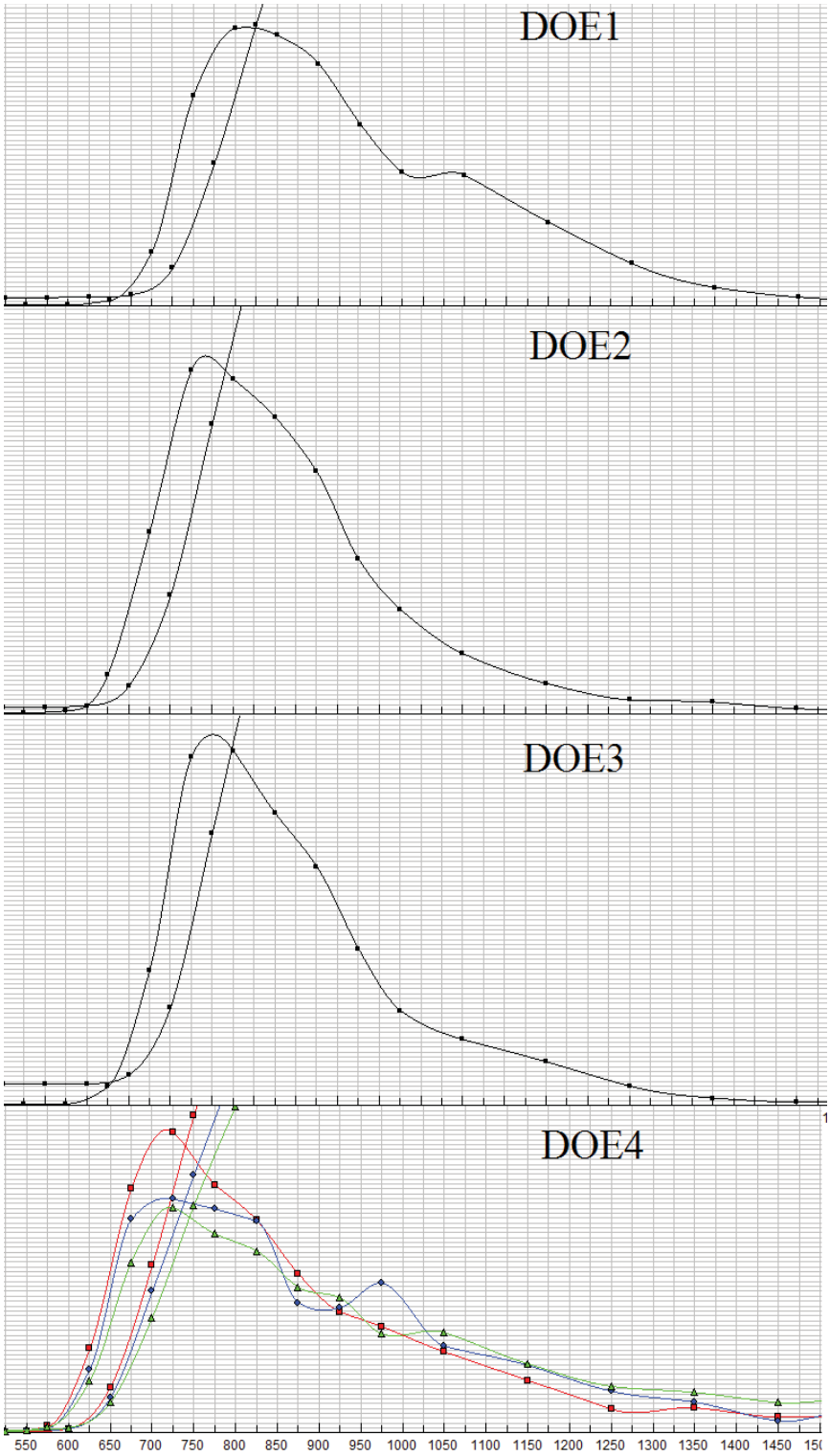


Figure XV. Density distribution – Particle diameter of DOE pellets (DOE1 – DOE4)

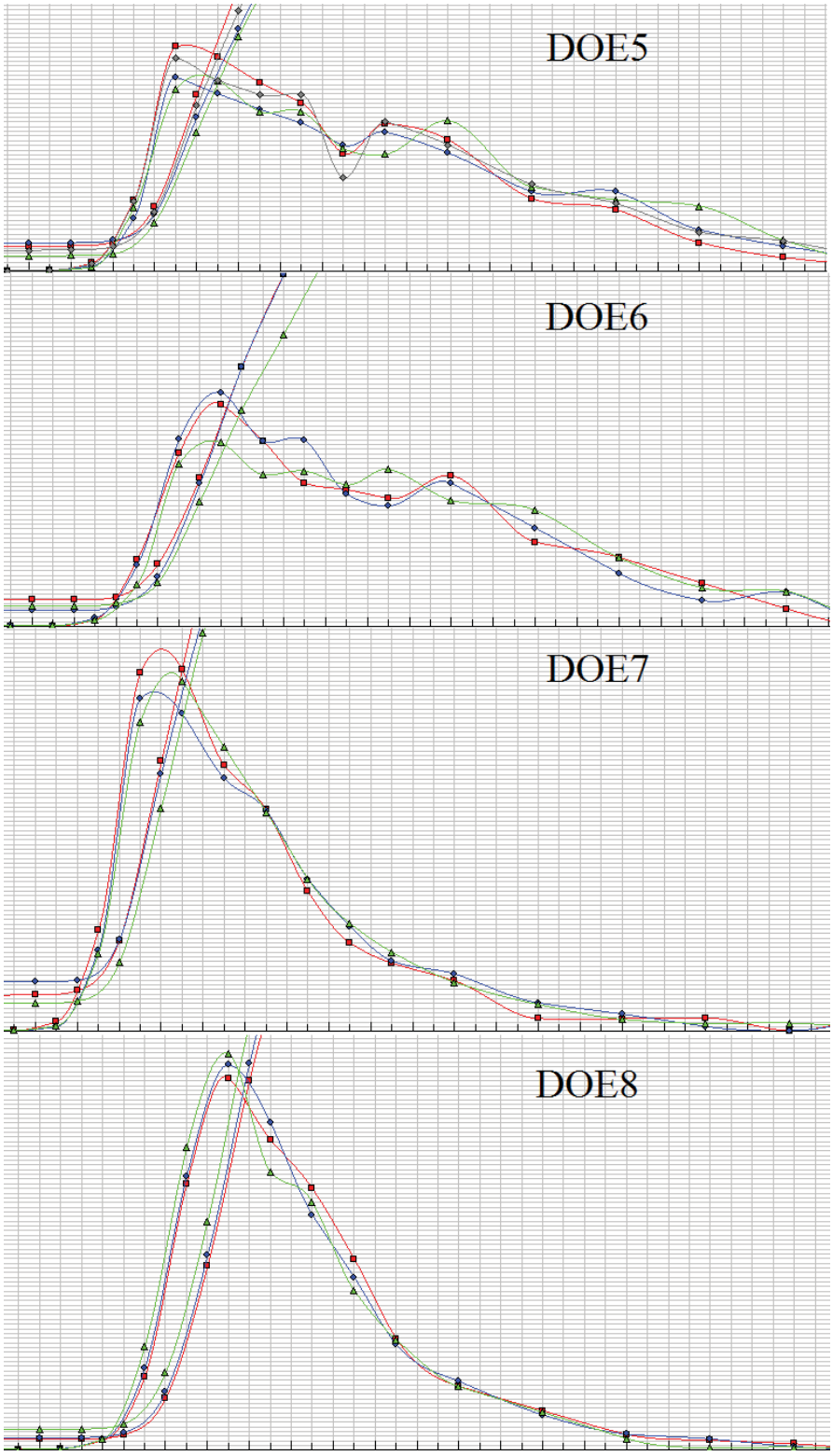


Figure XVI. Density distribution – Particle diameter of DOE pellets (DOE5 – DOE8)

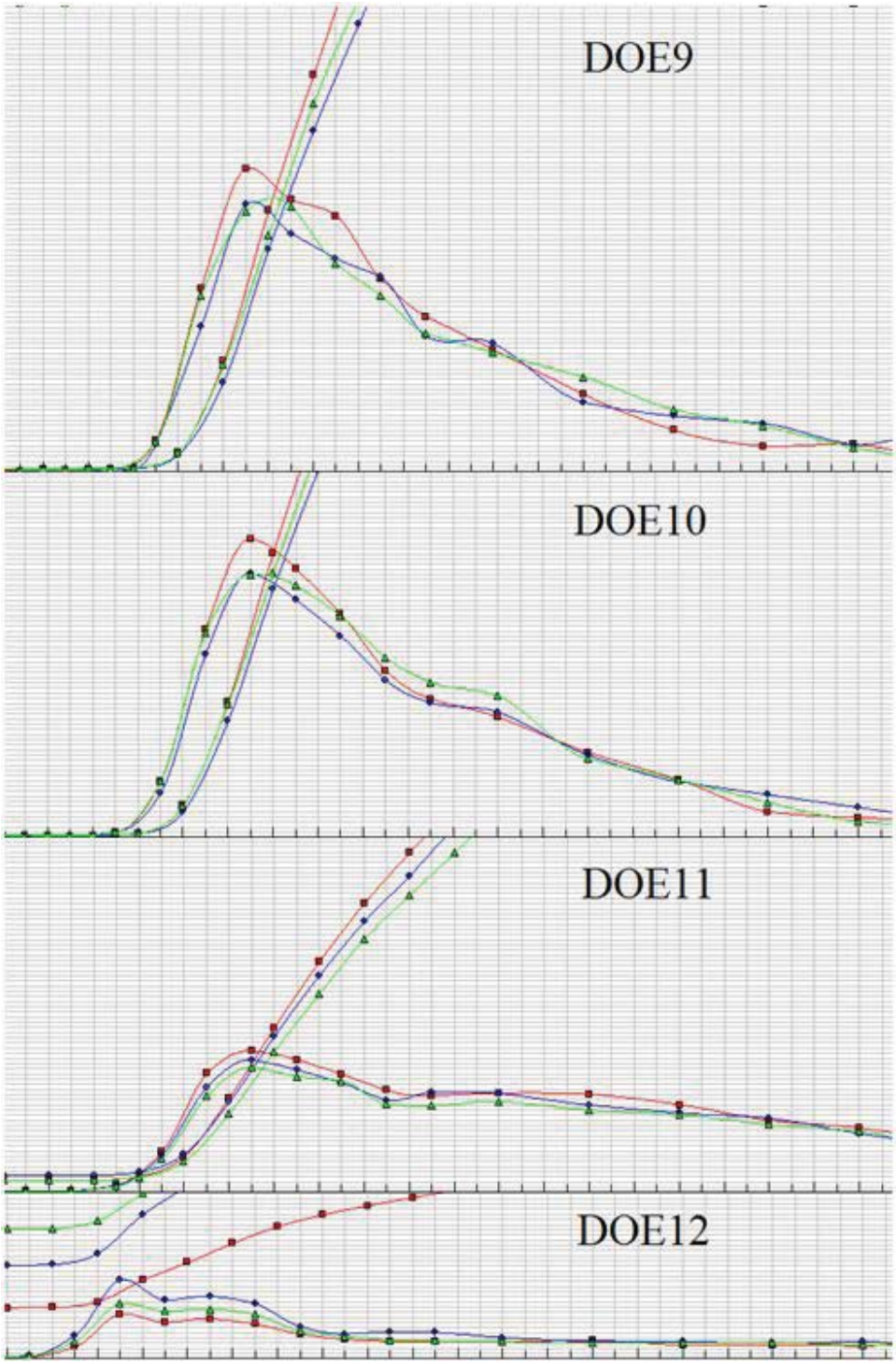


Figure XVII. Density distribution – Particle diameter of DOE pellets (DOE9 – DOE12)

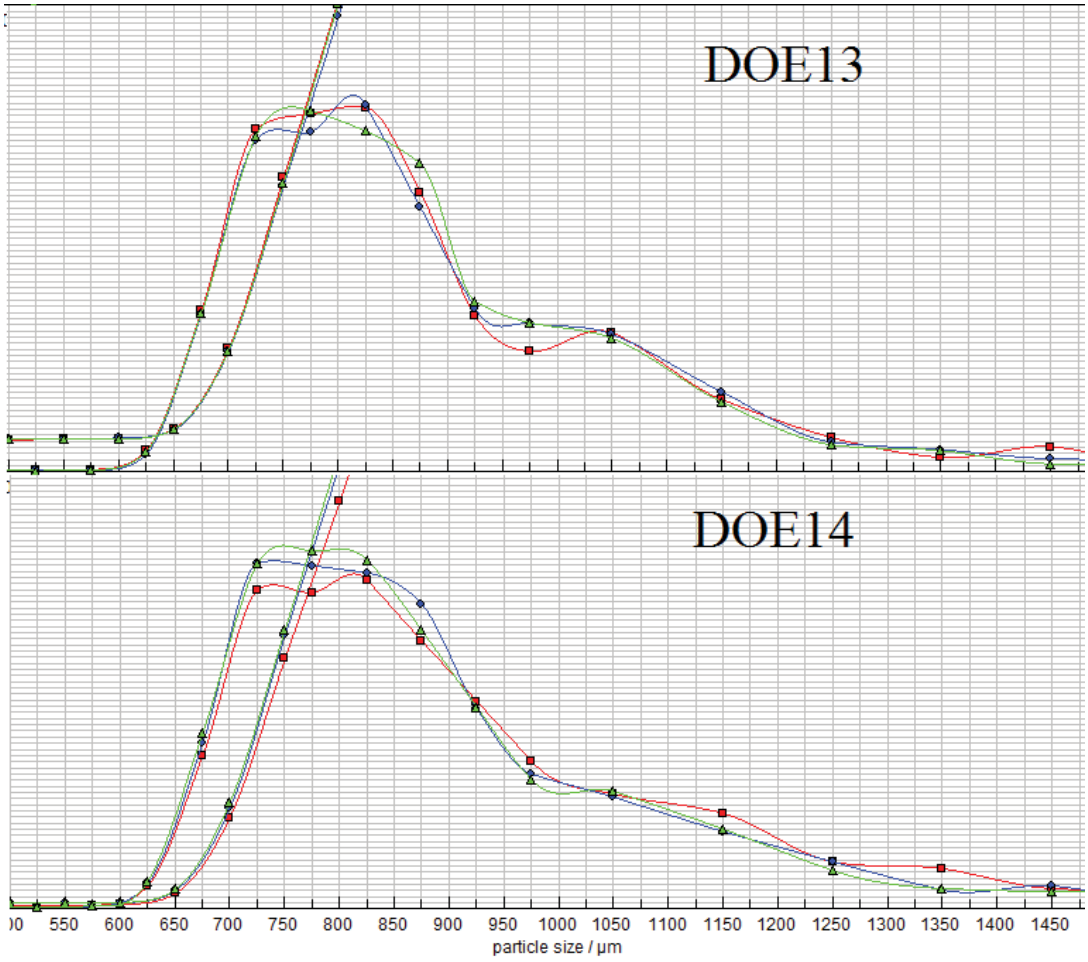


Figure XVIII. Density distribution – Particle diameter of DOE pellets (DOE13 and DOE14)

Appendix 7.

Table XIX. Sphericity values of the DOE batches

	Sphericity x10	Sphericity x50	Sphericity x90	Mean
DOE1	0.78	0.85	0.88	0.84
DOE2	0.85	0.88	0.90	0.88
DOE3	0.84	0.88	0.91	0.88
DOE4	0.82	0.87	0.90	0.86
DOE5	0.76	0.82	0.86	0.81
DOE6	0.75	0.82	0.87	0.81
DOE7	0.83	0.88	0.90	0.87
DOE8	0.84	0.89	0.91	0.88
DOE9	0.79	0.84	0.88	0.84
DOE10	0.79	0.84	0.88	0.84
DOE11	0.79	0.86	0.91	0.85
DOE11.3	0.81	0.86	0.91	0.86
DOE12	0.71	0.84	0.91	0.82
DOE12.2	0.81	0.86	0.90	0.86
DOE13	0.78	0.85	0.89	0.84
DOE14	0.83	0.88	0.90	0.87
mean	0.80	0.86	0.89	0.85
median	0.80	0.86	0.90	0.86
SD	0.04	0.02	0.02	0.02
min	0.71	0.82	0.86	0.81
max	0.85	0.89	0.91	0.88

Appendix 8.

Table XX. Measurement error of erosion rate method

Time (min)	DOE8 average HPMC released (g)	SD	DOE7 average HPMC released (g)	SD
15	6.27E-06	4.32E-06	3.71E-06	3.85E-07
30	7.02E-06	2.71E-08	6.50E-06	3.82E-07
45	9.25E-06	4.65E-08	8.81E-06	1.72E-07
60	1.09E-05	3.67E-07	1.05E-05	1.70E-07
90	1.28E-05	1.92E-07	1.22E-05	2.37E-07
120	1.40E-05	2.95E-07	1.32E-05	4.30E-07
150	1.49E-05	3.19E-07	1.41E-05	3.55E-07
180	1.56E-05	7.35E-08	2.41E-05	1.66E-05
210	1.62E-05	5.81E-08	1.50E-05	3.59E-07
240	1.65E-05	1.73E-07	1.52E-05	3.60E-07
300	1.68E-05	2.92E-07	1.55E-05	4.55E-07
360	1.68E-05	2.31E-07	1.53E-05	4.76E-07

Appendix 9.

Table XXI. Mass percentages of material accumulated in bottle during friability testing.

Batch ID	Meas. 1, % of pellet weight	Meas. 2, % of pellet weight	Meas. 3, % of pellet weight	Mean	SD
DOEN1	0.18	0.13	0.18	0.16	0.03
DOEN2	0.31	0.63	0.71	0.55	0.21
DOEN3	0.13	0.23	0.35	0.24	0.11
DOEN4	0.04	0.06	0.15	0.08	0.06
DOEN5	0.31	0.63	0.66	0.53	0.19
DOEN6	0.81	0.94	0.92	0.89	0.07
DOEN7	0.34	0.48	0.39	0.40	0.07
DOEN8	0.34	0.42	0.49	0.42	0.08
DOEN9	0.08	0.12	0.11	0.10	0.02
DOEN10	0.08	0.20	0.18	0.15	0.06
DOEN11	0.54	0.53	0.30	0.46	0.14
DOEN11.3	0.56	0.59	0.48	0.54	0.06
DOEN12	0.34	0.14	0.23	0.24	0.10
DOEN12.2	0.98	1.07	0.91	0.98	0.08
DOEN13	0.27	0.28	0.28	0.28	0.01
DOEN14	0.05	0.10	0.13	0.09	0.04
			Mean	0.38	0.08
			Median	0.34	0.07
			SD	0.27	0.06
			Min	0.08	0.01
			Max	0.98	0.21

Appendix 10.

Table XXII. Average pycnometric densities of DOE batches and re-measurement of DOE8.

Batch	Average pycnometric density (g/cm3)
DOE1	1.446375
DOE2	1.446375
DOE3	1.449975
DOE4	1.463775
DOE5	1.467125
DOE6	1.43575
DOE7	1.467025
DOE8	1.4322
DOE9	1.438625
DOE10	1.44725
DOE11	1.45805
DOE12	1.43905
DOE13	1.4492
DOE14	1.44785
mean	1.449188
SD	0.011221
-	1.437967
+	1.460408
DOE8_new	1.436367

Table XXIII. Average densities before and after curing

Batch	Average density (g/cm^3)	Average density after curing (g/cm^3)	Difference after curing (%)
DOE1	1.446375	1.442533	-0.266
DOE2	1.446375	1.4411	-0.365
DOE3	1.449975	1.441433	-0.589
DOE4	1.463775	1.455667	-0.554
DOE5	1.467125	1.4625	-0.315
DOE6	1.43575	1.4418	0.421
DOE7	1.467025	1.4873	1.382
DOE8	1.4322	1.446467	0.996
DOE9	1.438625	1.4539	1.062
DOE10	1.44725	1.461767	1.003
DOE11	1.45805		
DOE11.2	1.4407	1.430967	-0.676
DOE12	1.43905		
DOE12.2	1.442075	1.446267	0.291
DOE13	1.4492	1.451967	0.191
DOE14	1.44785	1.451133	0.227

Appendix 11.

Figure XXIV. LOD values of samples taken during the coating process